Cleveland Clinic Quarterly

Volume 27 April 1960 No. 2

THE DIAGNOSIS AND TREATMENT OF AMBISEXUALISM IN CHILDREN

RALPH A. STRAFFON, M.D.
Department of Urology

THE concept of what constitutes the sex of an individual has changed considerably in recent years. In most cases, the sex of a newborn infant is decided in the delivery room, and it is usually an obvious decision based on the type of external genitalia. In some instances, abnormal development of the external genitalia makes it difficult to determine the sex, and it is these cases of ambisexualism that are discussed in this paper.

Sex-Determining Factors

The primary factors that determine the sex of an individual are: (1) the chromosomal pattern of the individual cells; (2) the type of gonad; (3) the hormonal pattern and its effect on various tissues and organs; (4) the external genitalia, internal genital ducts, and secondary sexual characteristics; (5) the psychic reactions that are influenced by the environmental experiences of the individual. Since each person is a combination of the male and the female elements, it appears that the sex of any one person is the algebraic sum of all the factors mentioned above and not just any one of them.[1,2]

Types of Ambisexualism

Because of the problems in the clinical determination of sex, it is important to develop a working classification of ambisexualism. In general, patients whose sex is in question may be classified according to four large clinical groups: (1)

adrenogenital syndrome, (2) gonadal dysgenesis, (3) pseudohermaphroditism, and (4) true hermaphroditism.

Adrenogenital syndrome. Hyperadrenocorticism will produce any one of a variety of syndromes, but the discussion in this report will be confined to the adrenogenital syndrome in the female with virilization, since this is the syndrome that produces a problem of the differentiation of sex in the young child. In childhood the adrenogenital syndrome is the most common adrenal disorder, and more often affects females than it does males.

The adrenogenital syndrome may be due either to bilateral adrenal hyperplasia or to an adrenocortical tumor, but in the congenital form it is usually secondary to adrenal hyperplasia. There is considerable evidence that suggests the existence of a partial defect in the synthesis of hydrocortisone with an inability of the adrenal gland to convert 17-hydroxyprogesterone to hydrocortisone.[3-5] The lack of normal amounts of hydrocortisone stimulates increased release of corticotropin (ACTH) by the anterior pituitary, which would concomitantly cause an increase in production of androgen by the adrenal gland. These increased concentrations of androgen produce the virilization seen in the adrenogenital syndrome.

The increase in protein anabolism from the increased amounts of circulating androgen initially greatly accelerates growth, though the epiphyses close prematurely and the over-all effect is one of diminished stature. The excessive amounts of androgen interfere with the development of the external genitalia, and may result in hypertrophy of the clitoris, fusion of the labial folds, and diminution in the size of the vagina. Secondary sexual characteristics develop early with definite evidence of masculinization.[6]

Patients having adrenogenital dysfunction sometimes show additional signs associated with the adrenogenital syndrome. Approximately 30 per cent of these patients may present with an addisonian-like picture, and represent problems in electrolyte balance.[7] Another group of patients often have associated hypertension, and a third group has disturbances of carbohydrate metabolism.

Gonadal dysgenesis. Patients with gonadal dysgenesis may have either male or female sex chromosomes. Gonadal aplasia was described in 1938 by Turner,[8] who reported a group of girls with infantilism, cubitus valgus, and webbed neck. These were initially believed to be cases of ovarian agenesis, but later studies of sex chromosomes showed that the majority of these patients have the male configuration. These patients represent failure of gonadal development and genetically may be either male or female. Characteristically they are of small stature, have female external and internal genitalia, and sexual infantilism.[9]

The experimental work of Jost[10] revealed the mechanism involved in ambisexualism, particularly in those persons who have a male genotype and a female phenotype. He found that castration of fetal rabbits at an early stage in development, and replacement of the embryos into the amniotic cavity, resulted in female differentiation of the internal genital ducts and external genitalia. On the other

hand, removal of the ovary in no way affected the developing embryo. It thus appears that the morphogenetic substance of the fetal testes is necessary for differentiation of the male genital ducts and external genitalia. In gonadal aplasia the absence of secretions from the gonad permits female differentiation to occur whether the genetic sex is male or female.

Gonadal dysplasia (Klinefelter's syndrome) is characterized by male habitus, small testes, azoospermia, and gynecomastia. Persons with gonadal dysplasia often seek medical advice after puberty because of an infertility problem or the gynecomastia. Testicular biopsies show nearly complete fibrosis of the seminiferous tubules, but intact Leydig cells. The urine contains high concentrations of the follicle-stimulating hormone (FSH). The sex chromosomes were female in the majority of such persons, according to buccal smears.[11]

Del Castillo, Trabucco, and De la Balze[12] described a small group of patients having features similar to those seen in Klinefelter's syndrome, but without high concentrations of FSH in the urine. Testicular biopsies showed no germ cells, but intact Sertoli cells, and the majority of these patients had male sex chromosomes.

The factor producing a male gonad in a person of the female genotype may be an aberration in the chromosomes. It is postulated that the formation of an XXY or an XYY arrangement may be the cause.[13] Others believe that there may be inhibitory or damaging substances that suppress the cortical development of the gonad.

Pseudohermaphrodites. Persons whose genotypes and gonads are similar, but whose external genitalia suggest the opposite sex, are classed as pseudohermaphrodites. Male pseudohermaphrodites have male sex chromosomes and testicular gonadal tissue, but the external genitalia are ambiguous or female in type. This abnormality is best explained by assuming that the masculinizing hormones are abnormal or the tissues fail to respond to them. These patients may be divided into two groups: (1) those persons with ambiguous external genitalia, and in whom at puberty develop either male or female secondary sexual characteristics; and (2) those persons with female external genitalia. Persons in group 2 are often mistaken for normal females.[1]

Female pseudohermaphrodites without adrenal hyperplasia have female sex chromosomes and ovaries, but have masculinization of the external genitalia. This is a rare abnormality and is due to androgenic stimulation before complete development of the external genitalia. This has been reported[1] as having occurred in progeny of mothers with arrhenoblastomas or those receiving unusually large doses of progesterone during pregnancy.

True hermaphrodites. Persons who have both testicular and ovarian tissue are true hermaphrodites. The genotype may be either male or female, but the development of the external genitalia shows a great variety of gradations. About 70 cases of true hermaphroditism have been reported[14] to date.

Diagnosis of Ambisexualism

It is of paramount importance to investigate the patient with ambisexualism as early in his life as possible. The following abnormalities are indications for extensive study[2]: (1) deformity of the external genitalia; (2) hypospadias; (3) bilateral undescended testicles; (4) female external genitalia associated with palpable masses in the groin or labia majora.

Initally, sex-chromosome studies should be done on all patients in these groups. Among the first investigators in this field was Severinghaus,[15] who, using a complex procedure, identified the chromosomal sex in the nuclei of certain human cells. Barr, Bertram, and Lindsay[16] developed a more simplified technic that is practical and widely used today. By use of a special preparation, a mass of chromatin about one micron in diameter can be observed to lie against the inner surface of the nuclear membrane in from 50 to 90 per cent of cells examined in females, and from 0 to 20 per cent of cells in males. These chromatin masses can be identified in nearly all somatic cells, but epithelial cells obtained from buccal mucosal scrapings offer a reliable and satisfactory preparation. Whether this chromatin mass represents the adherence of 2X chromosomes or is something else is still a matter of great discussion.

After sex-chromosome studies are obtained, the group of patients with female pseudohermaphroditism secondary to adrenal hyperplasia must be differentiated from patients with other forms of ambisexualism. This can easily be done by obtaining a specimen of urine and determining the 17-ketosteroid excretion in a definite period, and also determining the concentration of pregnanediol.[6]

After the patients with adrenal hyperplasia have been identified, the determination of sex of the other patients becomes more complicated. Extensive studies of the anatomy must be made. A careful cystoscopic examination, looking for the presence of a vagina and cervix or a prostate, is a valuable diagnostic aid. Roentgen examinations, including the use of radiopaque material, as well as measurement of the urinary excretion of FSH and estrogens, are helpful in selected cases. After these preliminary studies have been carried out, it may be necessary to perform an exploratory operation and perform a biopsy on the gonads. When all the diagnostic findings are accumulated and evaluated, the sex-of-rearing can be determined and appropriate therapy instituted.

The selection of the sex-of-rearing should be based on the anatomic configuration of the external genitalia, particularly the size of the phallus or vagina and not primarily on the chromosomal or gonadal sex or structure of the internal genital ducts.[1] A female pseudohermaphrodite without adrenal hyperplasia is an exception to the above rule, provided a diagnosis is made in early infancy.

Extensive studies by psychiatrists interested in the problem of ambisexualism indicate that the sex toward which a child's upbringing is directed is the most important factor in the psychosexual orientation of the individual.[17,18] There is no evidence to indicate that bisexual or homosexual behavior develops more fre-

quently in ambisexual persons than in the general normal population.

Unfortunately when the sex of the external genitalia is doubtful, the decision as to the sex-of-rearing is sometimes delayed, producing confusion for both the child and his family. Psychologic studies indicate that alterations in the sex-of-rearing after two years of age frequently leave the patient in an unfortunate psychiatric state. When there is doubt regarding an infant's sex, this should be discussed immediately with the parents to prevent a public announcement of the sex of the child before it is confirmed. After the sex-of-rearing is decided on, it is again important to impress upon the parents that the child is a boy or a girl whose sexual organs were not completely differentiated at birth. This discussion must be carried on at the level determined by the intelligence of the parents. They must be told that it is most unlikely that their child will grow up with perverse sexual desires, for, in the layman's mind, ambisexualism is often confused with homosexualism.

Treatment of Ambisexualism

Female pseudohermaphroditism with congenital adrenal hyperplasia. In this syndrome the plan of therapy is to give fairly large doses of cortisone initially to obtain maximal adrenal suppression, and then to determine the minimal daily dose required for maintenance.[19] The initial dose is usually given intramuscularly for from 5 to 10 days, and then the appropriate maintenance dosage must be determined by following the patient with periodic 17-ketosteroid determinations and observations on bone growth and general development. Approximately one third of the patients with adrenogenital syndrome will have the electrolytic disorders seen in adrenal insufficiency. These patients must be hydrated with electrolyte solutions and treated with the appropriate steroids. Excessive steroids will produce a Cushingoid picture and a plateau in growth rate, so that the dosage used for maintenance must be constantly regulated.[20] These patients usually will recover from this salt-losing state and, as they grow older, supplemental steroids may not be required.

When the patient is two or three years of age, clitorectomy and separation of the fused labia majora should be performed.[21] When appropriate therapy is started early, growth and development occur at a normal rate. Those patients who have female pseudohermaphroditism secondary to adrenal hyperplasia but have been reared as males, should not be considered as being female. Plastic procedures can correct the hypospadias, and cortisone therapy given during childhood will prevent early epiphyseal ossification. Oophorectomy and hysterectomy will prevent feminization.

Gonadal aplasia. Persons with gonadal aplasia have infantile female internal and external genitalia. Fortunately, these persons are usually brought up as girls, although they may have male sex chromosomes.[22] Stunted growth, though frequently associated with this syndrome, is similar to that seen with primordial dwarfism for which there is no effective therapy. Plastic surgical procedures may

be necessary to correct some of the associated defects, such as the webbed neck seen in Turner's syndrome. When the patient is between 12 and 14 years of age, stilbestrol therapy is started, to permit normal endometrial development, breakdown, and menstruation. This therapy also produces rapid development of the breasts, labia, vagina, and uterus.[1]

Klinefelter's syndrome (gonadal dysplasia). In this syndrome, the testes are incapable of responding to gonadotropin. Often, sufficient androgens are produced to cause normal development of secondary sexual characteristics, but occasionally supplementary androgen therapy may be required. When present, gynecomastia does not respond to hormonal therapy; if it becomes a problem in management, mastoplasty may be performed.[23]

Male pseudohermaphroditism with external genitalia that resemble the female organs. Children with this abnormality usually develop feminine secondary sexual characteristics at puberty, but menstruation does not occur. These children should be reared as females, and orchiectomy should be performed, both to prevent any chance of masculinization and the development of malignant testicular tumors. After orchiectomy, supplemental estrogens may be given to allow normal female characteristics to develop, since the testes supply an important source of estrogen for these persons.[1]

Male pseudohermaphroditism with ambiguous genitalia. Children with this abnormality should be raised according to the functional ability of the external genitalia. If it is planned to raise the child as a female because of an exceedingly small phallus, orchiectomy should be performed fairly early to prevent possible masculinization. Plastic operative procedures should then be performed to make the genitalia conform as closely as possible to those of the female sex.

Female pseudohermaphroditism without adrenal hyperplasia. In children with this abnormality, normal female secondary sexual characteristics develop at puberty. It is important to recognize this syndrome early since these persons frequently may be raised as males. Clitorectomy and separation of fused labial folds are the only plastic procedures usually required.

True hermaphroditism. These hermaphrodites usually require the removal of the gonad that does not correspond to the sex-of-rearing. The remaining gonad will then usually direct secondary sexual development along the proper lines. In instances where ovotestes exist bilaterally, a part of each gonad may be removed. Often, plastic procedures are necessary to make the external genitalia conform as closely as possible to the sex-of-rearing.

Conclusions

Though hormonal treatment and the judicious use of surgical procedures are most important, the curative management of children with ambisexualism requires knowledge of the various entities that may produce this state, a great deal of

judgment in choosing the sex-of-rearing, and extraordinary understanding in treating both the child and his parents.

References

1. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. 2d Ed., Springfield, Ill.: Charles C Thomas, Pub., 1957, 526 pp.
2. Kiefer, J. H.: Recent advances in management of intersex patient. J. Urol. 77: 528-536, 1957.
3. Jailer, J. W.; Gold, J. J., and Wallace, E. Z.: Evaluation of "cortisone test" as diagnostic aid in differentiating adrenal hyperplasia from adrenal neoplasia. Am. J. Med. 16: 340-345, 1954.
4. Wilkins, L.; Gardner, L. I.; Crigler, J. F., Jr.; Silverman, S. H., and Migeon, C. J.: Further studies on treatment of congenital adrenal hyperplasia with cortisone. I. Comparison of oral and intramuscular administration of cortisone, with note on suppressive action of compounds F and B on adrenal. J. Clin. Endocrinol. 12: 257-276, 1952.
5. Eberlein, W. R., and Bongiovanni, A. M.: Partial characterization of urinary adrenocortical steroids in adrenal hyperplasia. J. Clin. Invest. 34: 1337-1343, 1955.
6. Wilkins, L.: Diagnosis of adrenogenital syndrome and its treatment with cortisone. J. Pediat. 41: 860-874, 1952.
7. Lewis, R. A.; Klein, R., and Wilkins, L.: Congenital adrenal hyperplasia with pseudohermaphrodism and symptoms of Addison's disease; clinical course following bilateral total adrenalectomy, with metabolic studies, pathologic findings and discussion of etiology. J. Clin. Endocrinol. 10: 703-715, 1950.
8. Turner, H. H.: Syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology 23: 566-574, 1938.
9. Wilkins, L., and Fleischmann, W.: Ovarian agenesis; pathology, associated clinical symptoms and bearing on theories of sex differentiation. J. Clin. Endocrinol. 4: 357--375, 1944.
10. Jost, A.: Embryonic Sexual Differentiation (Morphology, Physiology, Abnormalities). Chap. 2 *in* Jones, H. W., Jr., and Scott, W. W.: Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. Baltimore: Williams & Wilkins Co., 1958, 456 pp.
11. Nelson, W. O.: Sex differences in human nuclei with particular reference to Klinefelter syndrome, gonadal agenesis and other types of hermaphroditism. Acta endocrinol. 23: 227-245, 1956.
12. del Castillo, E. B.; Trabucco, A., and de la Balze, F. A.: Syndrome produced by absence of germinal epithelium without impairment of Sertoli or Leydig cells. J. Clin. Endocrinol. 7: 493-502, 1947.
13. Grumbach, M. M.; Blanc, W. A., and Engle, E. T.: Sex chromatin pattern in seminiferous tubule dysgenesis and other testicular disorders: relationship to true hermaphrodism and to Klinefelter's syndrome, with review of gonadal ontogenesis. J. Clin. Endocrinol. 17: 703-736, 1957.
14. Rosenthal, I. M.; Kiefer, J. H.; McGrew, E., and Bronstein, I. P.: Unilateral true hermaphroditism; two cases with sex-chromatin positive cellular pattern. Pediatrics 20: 1006-1019, 1957.
15. Severinghaus, A. E.: Sex chromosomes in human intersex. Am. J. Anat. 70: 73-93, 1942.

16. Barr, M. L.; Bertram, L. F., and Lindsay, H. A.: Morphology of nerve cell nucleus, according to sex. Anat. Rec. **107:** 283-297, 1950.

17. Money, J.; Hampson, J. G., and Hampson, J. L.: Examination of some basic sexual concepts: evidence of human hermaphroditism. Bull. Johns Hopkins Hosp. **97:** 301-319, 1955.

18. Money, J.; Hampson, J. G., and Hampson, J. L.: Hermaphroditism: recommendations concerning assignment of sex, change of sex, and psychologic management. Bull. Johns Hopkins Hosp. **97:** 284-300, 1955.

19. Blizzard, R. M., and Wilkins, L.: Present concepts of steroid therapy in virilizing adrenal hyperplasia. A. M. A. Arch. Int. Med. **100:** 729-738, 1957.

20. Wilkins, L.; Crigler, J. F., Jr.; Silverman, S. H.; Gardner L. I., and Migeon, C. J.: Further studies on treatment of congenital adrenal hyperplasia with cortisone. II. Effects of cortisone on sexual and somatic development, with hypothesis concerning mechanism of feminization. J. Clin. Endocrinol. **12:** 277-295, 1952.

21. Rosenwald, A. K.; Handlon, J. H.; Rosenthal, I. M.; Hyde, J. S., and Bronstein, I. P.: Psychologic studies before and after clitoridectomy in female pseudohermaphroditism caused by congenital virilizing adrenal hyperplasia. Pediatrics **21:** 832-839, 1958.

22. Grumbach, M. M.; Van Wyk, J. J., and Wilkins, L.: Chromosomal sex in gonadal dysgenesis (ovarian agenesis): relationship to male pseudohermaphrodism and theories of human sex differentiation. J. Clin. Endocrinol. **15:** 1161-1193, 1955.

23. Bunge, R. G., and Bradbury, J. T.: Newer concepts of Klinefelter syndrome. J. Urol. **76:** 758-765, 1956.

CONNECTIVE TISSUE DISEASE AND CARCINOMA OF THE PROSTATE TREATED WITH ESTROGENS

A Preliminary Report

ARTHUR L. SCHERBEL, M.D.
Department of Rheumatic Disease

IN reviewing the reports of coexistence of malignancy and a collagen disease, dermatomyositis and a form of arthritis clinically indistinguishable from rheumatoid arthritis are most frequently mentioned.[1] The typical triad of hypertrophic (pulmonary) osteoarthropathy characterized by clubbing of the digits, periostitis, and synovitis occurring in middle life, is well recognized as heralding the onset of a serious visceral disorder, frequently a peripheral bronchogenic carcinoma.[2]

Various neoplasms may coexist with dermatomyositis or arthritis of the rheumatoid type; these include carcinoma arising from the lung, stomach, breast, ovary, colon, and pleura. Other types of neoplastic disorders, such as Hodgkin's disease, multiple myeloma, and reticuloendotheliosis, have been reported[1] to be associated with one of the connective tissue diseases. It is well known that removal of the tumor often results in rapid and permanent improvement of the connective tissue disorder; however, if the primary lesion recurs, there may be reappearance of the connective tissue manifestations.

No report has been found in which carcinoma of the prostate was suspected of being related either to rheumatoid arthritis or to dermatomyositis. In this report, four cases are presented of carcinoma of the prostate gland and rheumatoid arthritis or dermatomyositis. The clinical course of these diseases suggests that a possible relationship exists between the neoplasm and the connective tissue disorders. Moreover, the favorable response to estrogen therapy in these patients is impressive, inasmuch as this form of treatment usually has no significant or lasting effect on rheumatoid arthritis,[3] except possibly on mild nonprogressive arthritis in menopausal women.[4]

Case Reports

Case 1. A 76-year-old man was first examined here because of intermittent swelling, redness, and aching in both wrists and in the dorsum of both hands for two months. He had mild pain in the right shoulder, the ankles, and the knees. During the acute phase, he stated that the pain in the hands was extremely severe and was only partially relieved by narcotics.

Three years before examination here he had acute urinary retention that was treated by a two-stage prostatectomy. One year later a gastric resection was performed after a massive hematemesis; the diagnosis was gastric ulcer. During the past five years, he had lost more than 20 pounds in weight. The only urinary difficulty remaining was a

mild nocturia (one to three times). There was no family history of arthritis or of genitourinary disease. The patient's mother died at age 51 years, of cancer of the stomach. There was no personal or family history of allergy.

At physical examination, the patient appeared gaunt and chronically ill. He weighed 128 pounds and his height was 68½ inches. There was moderate edema of the lower legs and feet. The interphalangeal joints of both hands were enlarged and the wrists were swollen, tender, and limited in motion. Digital examination of the prostate gland, revealed grade 1 enlargement, and a hard, nodular, fixed gland, which was confirmed by Dr. William J. Engel, Department of Urology.

Roentgenograms of the chest revealed slight left ventricular enlargement of the heart and bilateral emphysema. Roentgenograms of the pelvis showed evidence of osteoarthritis of the spine but not of metastatic bone lesions or calcifications in the prostatic area. There was some demineralization of the bones of the left wrist. Examination of the esophagus and stomach revealed good function of the gastric stoma. Results of intravenous urography were normal.

Laboratory studies showed an elevated erythrocyte sedimentation rate (0.95 mm. per minute by the Rourke-Ernstene method), and high concentration of serum acid phosphatase, 1.3 Bodansky units. Urinalysis, blood-urea, blood-sugar, serum-protein values and the albumin-globulin ratio were normal. Serum glycoprotein concentration (Shetlar) was high, 186 mg. per 100 ml. There was no free hydrochloric acid in the gastric fluid after histamine. The serologic test for syphilis was negative.

Stilbestrol, 1 mg. four times daily, was advised, and the patient returned home. Four weeks later it was observed that the joint manifestations had greatly improved. Thereafter he was examined monthly for five months, during which time the prostate became definitely smaller and softer on palpation. The serum gylcoprotein content was reduced to 142 mg. per 100 ml. and subsequently it dropped to 132 mg. His last examination here was six months after the first one, at which time he was asymptomatic; the dosage of stilbestrol was then reduced to 1 mg. three times daily. Two years later the patient's local physician reported that the patient was still receiving estrogen therapy and was asymptomatic. The following year, urinary symptoms recurred, complicated by metastasis to bone from the prostatic neoplasm. Joint manifestations recurred and persisted until the patient's death four months later.

Comment. In this elderly patient, the simultaneous improvement in joint manifestations and decrease in firmness and nodularity of the prostate were thought to be significant after the oral administration of stilbesterol. Two years later a second patient (case 2) was observed and it was decided to try intravenous estrogen therapy to find out whether or not joint manifestations would disappear even more rapidly than they did in the first patient.

Case 2. A 70-year-old man was examined because of migratory polyarthritis involving the knees, hips, shoulders, and metacarpophalangeal joints in both hands, which had been present for about a year. During the past three months, joint symptoms has been more severe, and during the past month, there had been a temperature elevation ranging from 99 to 100 F. He had received treatment with Butazolidin* (100 mg. four times daily) and hydrocortisone injections into the larger joints.

**Butazolidin (brand of phenylbutazone), Geigy Pharmaceuticals.*

At physical examination the patient appeared chronically ill, uncomfortable, and emotionally unstable. Blood pressure was 150/70 mm. of Hg. There was no evidence of disease in the lungs, heart, or peripheral vessels. The liver, spleen, and kidneys were not palpable. There were pain and restriction of motion in both shoulders, hips, and pain in both elbows. Metacarpophalangeal and interphalangeal joints and the knees were swollen and painful. The results of a neurologic examination were negative.

There was grade 2 enlargement of the prostate, which was moderately firm, but not hard or fixed; there were no palpable nodules. At the time of the initial examination the prostatic enlargement was thought not to be due to carcinoma, but a subsequent needle biopsy of the prostate revealed a well-differentiated adenocarcinoma, grade 2.

Urinalysis showed nothing abnormal. The hemoglobin was 10.4 gm. per 100 ml.; cell volume was 38 ml. per 100 ml. of blood. A leukocyte count was 10,000 per cu. mm., with 83 per cent neutrophils, 12 per cent lymphocytes, and 5 per cent monocytes. The serum acid phosphatase concentration was 2.66 Bodansky units. The serum protein value was 6.8 gm. per 100 ml.; serum albumin, 3.3 gm.; and serum globulin, 3.5 gm. per 100 ml. Erythrocyte sedimentation rate was 1.35 mm. per minute (Rourke-Ernstene).

The patient was given 1.0 gm. of Stilphostrol*, diluted in 1 liter of physiologic saline solution, intravenously daily for 10 days. Significant improvement manifested by disappearance of joint swelling and tenderness was noted by the fifth day. He was discharged from the hospital on the fourteenth day, at which time he had only minor aches and pains. Morning stiffness lessened from three hours to less than one-half hour at the time of discharge from the hospital. Continued therapy consisted of stilbestrol, 5 mg. daily, by mouth. A month later, joints were completely asymptomatic and joint stiffness had disappeared. At examination 10 months after discharge, general improvement was reflected in the results of laboratory tests: hemoglobin was increased to 13 gm. per 100 ml., cell volume to 44 ml. per kilogram of body weight, and the leukocyte count was reduced to 7,600 per cu. mm.

Comment. This patient has been re-examined every six months for five years, and the joints have remained entirely asymptomatic. The dosage of stilbestrol has been decreased to 1 mg. daily.

Case 3. A 70-year-old man was examined because of acute diffuse muscular aching and hot painful swelling in the metacarpophalangeal joints, which appeared three days previously. Two years and eight months before onset of joint manifestations a carcinoma of the prostate gland had been diagnosed with confirmation from specimens of a needle biopsy. During the subsequent 32 months, he had been treated with stilbestrol, 5 mg. twice daily, by mouth, and he became asymptomatic. Six months before the onset of the present musculoskeletal symptoms, he had an episode of urinary bleeding. Cystoscopy was performed at that time, and a low-grade cystitis and bleeding from prostatic varices were found. Since the hemorrhagic episode he had nocturia (two or three times). His personal history and his family history were negative for arthritis and for genitourinary disorders.

Physical examination showed swelling and painful limitation of motion in the metacarpophalangeal joints and in the ankles and knees. On digital examination, the prostate was stony hard and had poorly defined, irregular borders. Laboratory tests

**Stilphostrol (diethylstilbestrol diphosphate), Ames Co., Inc.*

disclosed that the hemoglobin was 10.8 gm. per 100 ml.; erythrocyte volume was 35 ml. per 100 ml.; leukocyte count was 4,800 per cu. mm., with 62 per cent lymphocytes (none immature), 33 per cent segmented neutrophils, 4 per cent eosinophils, and 1 per cent monocytes. Results of a latex fixation test were negative. The serum uric acid value was normal, as was the serum acid phosphatase, 0.6 Bodansky unit. The erythrocyte sedimentation rate was normal (Rourke-Ernstene method). Other laboratory findings, including the blood-urea and blood-sugar concentrations, and Wassermann and Kahn reactions, were normal.

Stilphostrol, 0.5 gm. diluted in 1 liter of physiologic saline solution, was administered intravenously daily for 10 days. After seven days there was complete clearing of joint symptoms, but morning stiffness lasting four hours persisted. The dosage of stilbestrol was increased to 5 mg. three times daily, taken orally, for maintenance therapy, and after one month the musculoskeletal symptoms had subsided completely.

Because of the persistence of anemia and of the abnormal leukocyte count, the bone marrow was examined five months later; it revealed evidence suggestive of a chronic monocytic leukemia (leukemic reticuloendotheliosis). Although stilbestrol was continued and the arthritic and prostatic symptoms did not recur, the patient died 18 months after the onset of joint symptoms, as a result of the progression of the leukemic process to an acute myelogenous form.

Comment. This patient is believed to be similar to those already described (cases 1 and 2) except for minor variations. Prostatic carcinoma was known to be present for 32 months (during which time the patient was treated with stilbestrol orally, 5 mg. twice daily). It is believed that the dosage was inadequate prior to the onset of joint manifestations, which disappeared rapidly after intravenous estrogen therapy.

Case 4. A 55-year-old man was first examined because of symptoms of about three months' duration: weakness of the arms and shoulders, and dermatitis of the face and anterior portion of the chest. Dermatomyositis had been previously diagnosed. The patient stated that he had had no cardiovascular, genitourinary, or gastrointestinal symptoms. His personal and family history were negative for rheumatoid arthritis and related disorders.

The patient was overweight: his height was 67½ inches and he weighed 200 pounds. The blood pressure initially was 160/110 mm. of Hg. There was severe weakness, and tenderness of the muscles of both shoulder girdles, winging of the scapulas, and weakness in both upper arms. He was unable to raise his arms above the shoulders. The thigh and gluteal muscles were also weak. Nonpitting edema was present over the forehead, the eyelids, and the zygomatic areas of the face. A deep-red, papular and papulopustular eruption resembling rosacea was on the face, and a deep-red, poikiloderma-like change was over the anterior part of the chest. Dull-red macules, and small, dry, rough plaques were on the dorsa of the hands and fingers. There was deep pitting edema of the lower legs and ankles. A mass of small lymph nodes was palpated in the left supraclavicular area. On digital rectal examination the prostate gland was firm but not fixed or nodular.

Biopsy study of a supraclavicular lymph node revealed adenocarcinoma, grade 3. A specimen of a needle biopsy of the prostate gland showed a similar adenocarcinomatous change. A biopsy specimen of muscle disclosed chronic myositis (compatible with

dermatomyositis) with edema, dense perivascular and interstitial infiltration of lymphocytes and plasma cells, piling up of nuclei of muscle fibers, and perivascular fibrosis. Some of the muscle fibers were pale and swollen, with diminished striation; other fibers were smaller than normal and were vesiculated. A biopsy specimen of skin from the left hand showed: hyperkeratosis and liquefaction degeneration of the basal layer, edema of the upper corium, and infiltration of lymphocytes and eosinophils in the mid-corium. Dermal appendages were surrounded by a similar infiltrate. Roentgenograms of the chest, the entire gastrointestinal tract, and the pelvis, revealed no evidence of neoplasm.

The serum protein determination (Tiselius method) showed: albumin, 1.99 gm.; alpha-1-globulin, 0.40 gm.; alpha-2-globulin, 0.53 gm.; beta-globulin, 0.75 gm.; gamma-globulin, 0.34 gm., and fibrinogen, 0.32 gm. per 100 ml. The serum transaminase (SGOT) values ranged from 20 to 75 units. The serum alkaline and acid phosphatase, blood-sugar and blood-urea values, routine urinalyses and Wassermann and Kahn reactions were normal. Several erythrocyte sedimentation rates were high, as were repeated serum glycoprotein determinations. The hemoglobin was 9.7 gm. per 100 ml. with normal total and differential leukocyte counts. The 24-hour creatine excretion was 0.224 gm., and the creatinine excretion was 1.49 gm.; several times similar results were obtained.

Stilphostrol was administered intravenously, and the initial course of a total dose of 7 gm. given within 10 days brought about dramatic improvement with decreased edema, increased strength, and clearing of the skin lesions. Oral therapy with 10 mg. per day of stilbestrol was started. One month later when the patient returned for evaluation, he appeared to be in relapse. He was readmitted to the hospital for a second course of intravenous estrogen therapy; this time he received a total dose of 5 gm. in 10 days, again with good subjective and objective responses. Because large doses of estrogens only partially controlled the disease, prednisone, 2.5 mg. three times daily, was added to the regimen. During the next three months he gradually regained strength and the skin lesions cleared completely. Chloroquine phosphate* was started; the dosage of prednisone was reduced to 1 mg. three times daily; and estrogen maintenance therapy was continued. Improvement continued, and the patient returned to work about one year after therapy was started, and then was lost to follow-up.

Comment. This is an unusual case because carcinoma of the prostate is associated with dermatomyositis. The response to intravenous estrogen therapy was similar to that of patients with rheumatoid arthritis associated with carcinoma of the prostate.

Treatment and Results

Estrogen therapy was used for all patients. Three of the four patients were followed for from two to five years; one was observed for two years, and then was lost to follow-up. One patient (case 1) received estrogen only by mouth; one (case 3) who was already receiving estrogen when first examined was given additional intravenous estrogen therapy (Stilphostrol); and two patients (cases 2 and 4) received intravenous estrogen therapy (0.5 to 1.0 gm. daily for 10 days), followed by stilbestrol orally, 5 mg. daily. In the one patient who received only oral therapy, significant improvement occurred after four to six weeks. Improve-

**Aralen phosphate (chloroquine phosphate), Winthrop Laboratories.*

ment was more rapid in the two patients who received estrogen intravenously, with significant change occurring between the seventh and twelfth days after beginning the treatment. One patient (case 4) required an additional course of estrogen intravenously before significant improvement persisted.

The erythrocyte sedimentation rate was increased in each patient, and serum protein alterations were manifested by decreased serum albumin and increased serum globulin values. In all patients serum glycoprotein values (Shetlar) were elevated and returned to normal after therapy. Two patients were examined before the latex fixation test was available; in the other two patients the test was negative. In two patients, the acid phosphatase values were high before treatment and returned to normal after estrogen therapy. One patient (case 3) had been receiving stilbestrol orally for more than two years, when first examined here, and his acid phosphatase value was normal. The patient with dermatomyositis (case 4) also had a normal acid phosphatase value, despite distant metastasis to cervical lymph nodes.

In order to evaluate further the effect of Stilphostrol therapy in patients with rheumatoid arthritis, a comparable group of five men and four women with active rheumatoid arthritis (stage I or stage II), whose functional capacity ranged between 1 and 3, were hospitalized to receive intravenously Stilphostrol, 0.5 to 1.0 gm., in 1 liter of 5 per cent dextrose daily for 10 days. During the second week of therapy, mild, temporary improvement manifested by lessening of pain, of swelling, and of inflammation of joints occurred in two men and in one woman, but in no instance was improvement as impressive or as permanent as it was in the patients with neoplasm of the prostate. For this reason, it is believed that intravenously administered estrogen does not exert a significant or selective antirheumatic effect in patients with rheumatoid arthritis.

Discussion

Carcinoma of the prostate is a common disease in men of advanced age. In a reported autopsy series,[5] histologically demonstrable prostatic carcinoma was present in 12.5 per cent in the 50 to 60 year age group, and in 33.1 per cent of those in the 80-year age group. However, clinical diagnosis of prostatic carcinoma was made in only one sixteenth of the cases, and clinical evidence of metastasis was present in only one third of the cases that were correctly diagnosed before death. On the other hand, it is well recognized that rheumatoid arthritis usually appears relatively early in life and in only about 10 per cent of the patients for the first time after the sixth decade.

All four patients had symptoms that suggested urinary obstruction; in addition, one patient previously had a transurethral resection for obstructive symptoms and one had an infection of the urinary tract when he was first examined at the Clinic. On palpation the prostate was typical of neoplasm in only two of the four patients; those glands were firm, fixed to surrounding tissue, and nodular. In one

patient (case 2), the gland was moderately firm only along the left lateral border, and study of a specimen of a needle biopsy was necessary for diagnosis. The prostate gland of the patient with severe dermatomyositis (case 4) was normal to palpation at the time of the initial examination, but enlarged cervical lymph nodes revealed metastatic carcinoma suggestive of prostatic neoplasm, and a subsequent specimen of a needle biopsy of the prostate gland confirmed the diagnosis.

It is possible that these patients with musculoskeletal symptoms had two unrelated diseases that developed simultaneously, but this appears unlikely for several reasons. No patient had a family history of rheumatoid disease. Musculoskeletal manifestations appeared for the first time relatively late in life, usually shortly after the onset of the urinary symptoms; and furthermore, therapy administered primarily to control the prostatic neoplasm resulted in great improvement or in disappearance of muscular and joint symptoms along with shrinking and softening of the neoplasm.

In each patient musculoskeletal manifestations were moderately severe and progressive. Joint disturbances in three patients (cases 1-3) were clinically indistinguishable from those of typical progressive rheumatoid arthritis. However, in one patient (case 3), there was roentgen evidence of periosteal involvement of the long bones; this suggested hypertrophic osteoarthropathy. In no patient was there clubbing of the fingers. The patient with dermatomyositis (case 4) had severely progressive disease that was unresponsive to previous corticosteroid therapy; subsequently intravenous estrogen therapy resulted in significant improvement.

The mechanism of the uniform clinical improvement with respect to the musculoskeletal manifestations in these patients is not understood. In the past, numerous chemical agents have been recommended in the treatment of rheumatoid arthritis, but no agent is consistently effective for long periods, especially when the disease is progressive.[6]

It has been reported[7] that stilbestrol is an effective cytotoxic agent. It is possible that the intravenous administration of Stilphostrol exerts a nonspecific toxic effect on certain mesenchymal cells in patients with connective tissue disorders, which is independent of the estrogenic properties of the hormone.

Carcinoma arising from prostatic epithelium is more or less dependent for its growth on androgenic hormones, but the exact mechanism by which estrogens suppress prostatic carcinoma is not understood. There may be a direct action on prostatic tissue, or the benefits may be derived from the inhibition of pituitary production of gonadotropins in the intact patient. However, evidence has been presented[8] suggesting that the pituitary-testis-adrenal mechanism is not a factor since improvement has occurred in patients who have had both orchiectomy and adrenalectomy.

In those patients who exhibited significant improvement in musculoskeletal manifestations after estrogen therapy, changes also occurred in the prostatic neo-

plasm as manifested by a decrease in size, disappearance of nodules and softening of the prostate gland. Moreover, it was also observed that recurrence or worsening of musculoskeletal symptoms after a prolonged period of improvement of from one to two years was associated with recurrence and spread of the prostatic neoplasm (case 2). One patient (case 3) had had urinary symptoms and known carcinoma of the prostate for 32 months before the onset of acute polyarthritis. He had been taking stilbestrol orally, 5 mg. daily, since identification of the neoplasm, and urinary symptoms were not apparent when musculoskeletal symptoms appeared. Additional intravenous estrogen therapy with Stilphostrol brought about complete regression of joint pain and swelling during the first week of therapy.

The concept of an immunologic mechanism involving circulating antibody which affects pathogenesis, has led to the search for gamma-globulin in various rheumatic lesions.[9] Recently it was reported[10] that patients with disorders of connective tissue often sustain exaggerated reactions to the biogenic amines, serotonin and histamine, both of which are thought to be important agents in allergic, immunologic, and anaphylactoid disorders. These clinical and experimental observations suggest that rheumatoid arthritis and dermatomyositis may occur as a secondary manifestation or host reaction to carcinoma of the prostate. These diseases are closely similar to the connective tissue diseases that have been reported to occur after other forms of neoplastic disease are evident. Apparently almost any malignant neoplasm is capable of inducing this syndrome, and treatment, whether it be by surgical removal, chemotherapy, or irradiation, if it is effective in suppressing the neoplasm, results in alleviation of the connective tissue reaction. At present, we have under observation several women with carcinoma of the breast and rheumatoid arthritis who are receiving testosterone therapy.

Summary

Three patients who sought treatment for rheumatoid arthritis that began after age 60 years, were found to have carcinoma of the prostate gland. A fourth patient, aged 55 years, in whom the typical clinical and pathologic features of dermatomyositis developed, also had carcinoma of the prostate gland. All four patients received estrogen therapy, and those patients with rheumatoid arthritis and prostatic carcinoma responded with complete disappearance of their rheumatic symptoms; the patient with dermatomyositis responded significantly but incompletely.

References

1. Lansbury, J.: Collagen disease complicating malignancy. Ann. Rheumat. Dis. **12:** 301-305, 1953.

2. Vogl, A.; Blumenfeld, S., and Gutner, L. B.: Diagnostic significance of pulmonary hypertrophic osteoarthropathy. Am. J. Med. **18:** 51-65, 1955.

3. Hellbaum, A. A.; Ishmael, W. K.; Duffy, M. L., and Payne, R. W.: Effect of estrogen, androgen, and thyroid in degenerative joint disease. J. Gerontol. **13:** 163-166, 1958.

4. Ishmael, W. K.: Oral stilbestrol therapy in menopause arthritis. Soc. Proc., J. A. M. A. 117: 1650, 1941.

5. Birke, G.; Franksson, C., and Plantin, L.-O.: Carcinoma of prostate: clinical and steroid metabolic study. Acta chir. scandinav. 109 (Fasc. 2): 129-149, 1955.

6. Scherbel, A. L.: Rational appoach to treatment of rheumatoid arthritis: introduction. Cleveland Clin. Quart. 24: 69-70, 1957.

7. Taylor, J. R.: Intravenous and oral trial of stilboestrol diphosphate in prostatic carcinoma. Canad. M. A. J. 80: 880-882, 1959.

8. Flocks, R. H.; Marberger, H.; Begley, B. J., and Prendergast, L. J.: Prostatic carcinoma: treatment of advanced cases with intravenous diethylstilbestrol diphosphate. J. Urol. 74: 549-551, 1955.

9. Kaplan, M. H.: Fluorescent antibody technic as research tool in study of connective tissue disease. Arth. & Rheumat. 2: 568-573, 1959.

10. Scherbel, A. L., and Harrison, J. W.: Response to serotonin and its antagonists in patients with rheumatoid arthritis and related diseases. Angiology 10: 29-33, 1959.

THE ARTIFICIAL KIDNEY FOR ACUTE GLUTETHIMIDE (DORIDEN*) AND BARBITURATE POISONING

Report of Four Representative Cases

SATORU NAKAMOTO, M.D.,† and WILLEM J. KOLFF, M.D.
Department of Artificial Organs

THE artificial kidney has been used successfully in acute poisoning in a number of patients.[1-5] Hemodialysis appears to be a rational and effective treatment of acute toxicity caused by ingestion of excessive amounts of barbiturate, glutethimide, salicylate, bromide, diphenylhydantoin sodium, bichloride of mercury, or mushroom poisons.

In treating poisoning from hypnotic drugs the goal of dialysis is twofold: to eliminate the poison and to shorten coma. Patients can be allowed to sleep out their barbiturate effects as long as respiration, blood pressure, and temperature are under control. In a light case of barbiturate poisoning, we let the patient sleep, but observe him closely so as to be able to ward off complications. The clinical intervention with hemodialysis is justified in two conditions: (1) when the amount of poison ingested or the initial concentration of poison in the blood is unquestionably in the fatal range, and (2) when the underlying physical state of the patient dangerously heightens the risk of prolonged sleep or coma. The time required to assemble a Kolff twin-coil artificial kidney[6,7] and the risk of hemodialysis to the patient are negligible when the procedure is performed by an experienced team. The reduction of morbidity is as legitimate an indication for the use of the artificial kidney as is the reduction of mortality.

Our report concerns four representative cases of acute poisoning from hypnotic drugs that do not cause much direct damage to the kidneys. Two of the patients had glutethimide poisoning and two of the patients had barbiturate poisoning. The four patients underwent a total of seven dialyses with the Kolff twin-coil kidney. The usual methods to maintain comatose patients were employed. A large amount of fluid was intravenously administered during and after dialysis in order to obtain the maximal urinary excretion of poison. The amount of fluid was adjusted from an hourly measurement of urinary output, and the amount of electrolytes in solution was estimated from a urinary electrolyte determination. In the patients who required tracheotomy for respiratory difficulty before dialysis, regional heparinization was applied to prevent excessive bleeding from the surgical wound.[8] By means of Goldbaum's technic[9,10] the blood or plasma concentrations of glutethimide or barbiturate were determined before and after each hemodialysis by Dr. Irving Sunshine, technical director and toxicologist in the Cuyahoga County Coroner's Office.

**Doriden (glutethimide N.N.R. Ciba), Ciba Pharmaceutical Products, Inc.*
†Fellow in the Department of Artificial Organs.

Case Reports

Case 1. *Glutethimide poisoning.* A 48-year-old housewife in a state of coma for approximately five hours was admitted to a local hospital. For the previous four years she had been under a psychiatrist's care. She had ingested approximately 15 tablets of glutethimide (Doriden, 0.5 gm. per tablet) and an unknown number of phenobarbital tablets (150 mg. per tablet). The lethal dose of glutethimide for human patients ranges from 10 to 20 gm.[4] Gastric lavage was performed in the emergency room. Deep-tendon reflexes were present but shortly disappeared. The respiration was maintained through an endotracheal tube. Levophed* was administered intravenously to maintain adequate blood pressure. Having been treated conservatively for approximately 24 hours without improvement in her condition, she was transferred to the Cleveland Clinic Hospital for treatment with the artificial kidney.

When we first examined the patient, her blood pressure was 120/68 mm. of Hg during the continuous infusion of Levophed. Respirations were slow and shallow. The pupils were equal and dilated. The patient appeared completely flaccid without deep-tendon reflexes. There was no response to painful stimuli. The initial concentration of glutethimide in the blood was reported as 3.9 mg. per 100 ml., and no barbiturate was detected. She immediately underwent treatment with the artificial kidney for eight hours. At the end of dialysis the amount of glutethimide in the blood was 1.9 mg. per 100 ml. She was able to move the extremities. *Figure 1* is a graph of

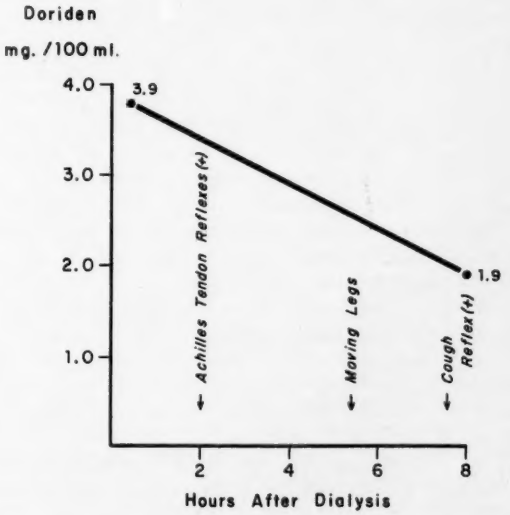

Fig. 1. Case 1. Clinical and chemical status of a 48-year-old woman with glutethimide (Doriden) poisoning after treatment with the artificial kidney.

**Levophed (levarterenol bitartrate), Winthrop Laboratories.*

the clinical and chemical status during dialysis. The postdialytic course was uneventful and she was discharged on the twentieth hospital day.

Comment. This patient had severe glutethimide poisoning, having ingested approximately 7.5 gm. of Doriden and an unknown amount of phenobarbital. The possible synergism of barbiturate cannot be assessed. She underwent continuous clinical deterioration, manifested by coma, respiratory difficulty, and hypotension, athough she had a short period when deep-tendon reflexes were present. She recovered from acute poisoning by means of hemodialysis.

Case 2. *Glutethimide and barbiturate poisoning.* A 56-year-old housewife, known to have depressive psychosis for the past 12 months, was found in her home in a coma of about four hours' duration. Empty bottles of Doriden, Butiserpine* and Quiactin† were nearby on the floor. Evidence of crushed medicine was found around her mouth, in a glass, in the sink, and on the floor. The amount of ingested drugs was unknown. She was taken to a hospital and was given gastric lavage, amphetamine sulfate (Benzedrine‡), 40 mg. intravenously, as a stimulant, and intubation for respiratory difficulties. After these emergency treatments she was transferred to the Cleveland Clinic Hospital for treatment with the artificial kidney. When first examined the blood pressure was 90/50 mm. of Hg. Respirations were slow and shallow. The pupils were dilated and were fixed. She was completely flaccid and had some hyperactive deep-tendon reflexes. Hoffmann's sign was present bilaterally. The Babinski reflex was absent, but ankle clonus was present. In our emergency room the patient received a large amount of Megimide§ and Benzedrine without apparent response. Hypotension developed shortly after she was admitted, and Levophed was necessary to maintain the blood pressure. Respiration was maintained with a Bennett respirator. As the conservative treatment had failed, about three hours after admission she was treated with the artificial kidney for nine hours; there was slight clinical improvement. During hemodialysis she began to breathe spontaneously. The blood pressure was maintained without administering vasoconstrictors. The pupil reflexes were sluggish, but the corneal reflex remained absent. The next day a small amount of Levophed again was required to maintain blood pressure, and she underwent a second treatment with the artificial kidney for five hours, but without apparent improvement. The pupils did not react, and deep-tendon reflexes were sluggish. The cough reflex could be elicited after the second dialysis. The patient remained in deep coma, and areflexia persisted until the sixth day of hospitalization, when she underwent the third dialysis for six hours; there was no improvement. She underwent artificial hibernation for the last two days without success. She died about 10 hours after the termination of the third dialysis.

The barbiturate concentration in the blood was as follows: prior to the first dialysis, 1.6 mg. per 100 ml., at the end of dialysis, 0.9 mg.; prior to the second dialysis, 0.5 mg. per 100 ml.; no barbiturate was detected at the end of the second dialysis. Before the first dialysis Doriden was not found in the blood but was in the urine. At necropsy

**Butiserpine (butisol sodium, butabarbital sodium, reserpine), McNeil Laboratories, Inc.*

†Quiactin (oxanamide: 2-ethyl-3-propylglycidamide), The Wm. S. Merrell Company.

‡Benzedrine sulfate (amphetamine sulfate), Smith Kline & French Laboratories.

§Megimide (β-ethyl-β-methylglutarimide), Abbott Laboratories.

there was no evidence of barbiturate in the blood. *Figure 2* is a chart showing the clinical and chemical status during and after dialysis. The coroner reported the cause of death as: (1) synergistic effect of glutethimide and barbiturate, (2) bilateral pneumonia, and (3) bilateral hydrothorax and hydropericardium.

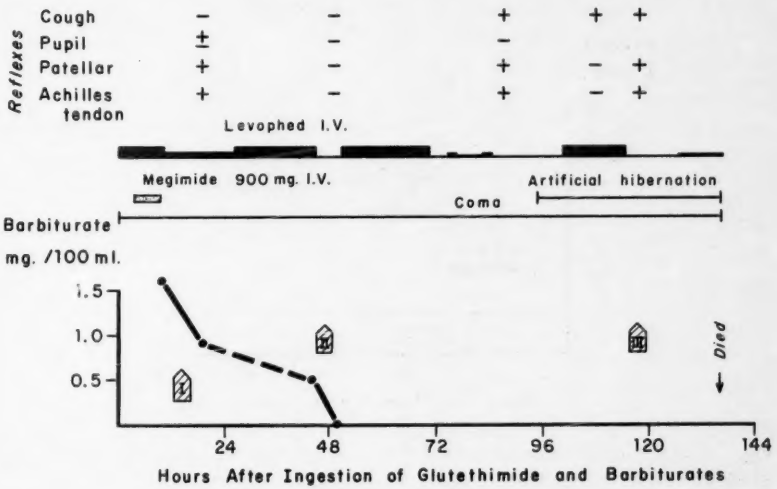

Fig. 2. Case 2. Clinical and chemical status of a 56-year-old woman with glutethimide and barbiturate poisoning after treatment with the artificial kidney and artificial hibernation, and to death. I, II, and III = dialyses.

Comment. This patient ingested unknown doses of several drugs, such as Doriden, and presumably Butiserpine and Quiactin; the role of Butiserpine and Quiactin cannot be assessed. Doriden was not found in the blood sample but in urine, which was collected during dialysis. The synergistic effect of a combination of drugs and secondary pneumonia may have led to the irreversible state, despite removal of toxic substances by three dialyses. In retrospect, perhaps the three dialyses should have been given in rapid succession.

Case 3. *Secobarbital poisoning.* A 75-year-old man known to have depressive psychosis for the past year was admitted to the Cleveland Clinic Hospital in a coma of six hours' duration. He had ingested about 40 tablets of secobarbital (Seconal,* 100 mg. per tablet). He appeared to be in shock with a blood pressure of 60/40 mm. of Hg. Respirations were rapid and shallow. He was completely flaccid with no deep-tendon reflexes. Pupils were dilated and were fixed. The corneal reflex was absent. Gastric lavage was performed immediately. For the next eight hours he was treated conservatively, and within four hours showed some clinical improvement by responding to

**Seconal (secobarbital), Eli Lilly and Company.*

painful stimuli. Deep-tendon reflexes were present. He became hypotensive and required the administration of Levophed.

Because of no improvement with the conservative management, he was treated with the artificial kidney for seven hours. *Figure 3* is a chart showing the clinical and chemical status during and after hemodialysis. The next day a tracheotomy was performed.

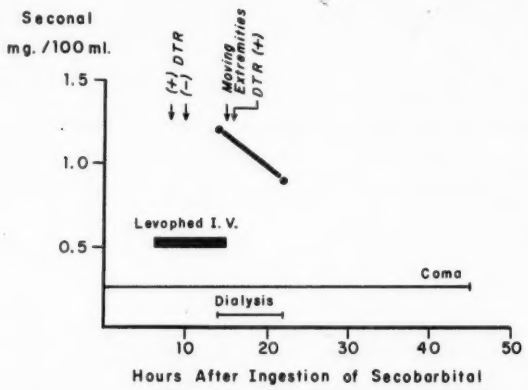

Fig. 3. Case 3. Clinical and chemical status of a 75-year-old man with secobarbital poisoning after treatment with the artificial kidney.

He began to respond and became relatively alert on the second day after dialysis; he remained oliguric for three days after dialysis. The remaining course was uneventful and the patient was discharged on his thirtieth hospital day.

Comment. This patient had severe secobarbital poisoning. He was treated conservatively for about eight hours after admission to the hospital but continued to deteriorate clinically. The slow recovery after seven hours of dialysis was probably due to generalized cerebral arteriosclerosis and to his age. There was no evidence of underlying complications in this patient. Hemodialysis relieved him of the severe toxicity.

Case 4. *Barbiturate poisoning.* A 46-year-old housewife with known systemic lupus erythematosus and recent mental depression was admitted to the Cleveland Clinic Hospital because of coma of about five hours' duration from possible barbiturate poisoning. No information was available as to what type of barbiturates had been ingested or the dosage. Respiration was gasping at first, then ceased entirely. Intubation was immediately applied. Blood pressure was 90/70 mm. of Hg. Pupils were dilated and were fixed. The patient was completely flaccid without deep-tendon reflexes and response to painful stimuli. In order to rule in or out a cerebral lesion, a spinal puncture was performed; the fluid specimen was reported as normal. A Bennett respirator was necessary to support the pulmonary ventilation. Shortly after admission, the artificial kidney was used for eight hours without apparent improvement. The respirator still was needed to maintain adequate air exchange, and the infusion of Levophed was needed

to support the blood pressure. About nine hours after termination of the first dialysis a second treatment with the artificial kidney was given for nine hours. During the second dialysis, clinical improvement was evident; the patient began to maintain her own blood pressure as well as respiration. *Figure 4* is a chart showing the clinical and chemical status of the patient during and after dialysis. The remaining course was uneventful and she was discharged on her twenty-seventh hospital day.

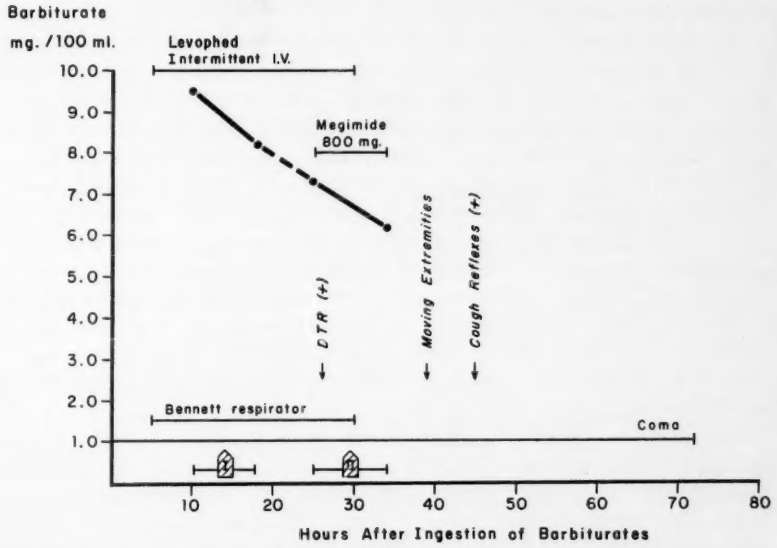

Fig. 4. Case 4. Clinical and chemical status of a 46-year-old woman with presumably barbiturate poisoning after treatment with the artificial kidney. I and II = dialyses.

Comment. This patient had severe barbiturate poisoning with a possible synergism of other drugs the role of which can neither be assessed nor be excluded from consideration. The first dialysis did not result in clinical improvement, and a second dialysis was necessary to obtain recovery from the acute poisoning.

Discussion

Each of our four patients with acute drug poisoning was first treated with the usual conservative supportive management, such as gastric lavage, correction of airway obstruction, artificial respiration through an endotracheal tube, and treatment of shock with intravenous infusion of drugs to restore an adequate blood pressure. In the absence of improvement with the conservative management the artificial kidney was used in the hope that hemodialysis would reverse the toxic

state. A large amount of fluid was given intravenously to each patient during and after dialysis to promote excretion of the drugs through the patient's own kidneys. The amount of fluid and electrolyte intake was determined by hourly measurement of urinary output and urinalysis for electrolytes, such as sodium, chloride, and potassium. There was no evidence of postdialytic oliguria as seen in chronic renal failure,[11] except in one patient (case 3). That patient with secobarbital poisoning remained oliguric (urinary output was less than 500 ml. per day) for three days after dialysis.

When the patient's clinical condition rapidly deteriorates despite the conservative measures mentioned, along with well-maintained artificial respiration, hemodialysis must be done without delay. A patient whose condition is not rapidly deteriorating should be allowed to sleep off the sedative effects, and his circulation and respiration should be closely observed and supported to prevent decubitus. A sicker patient should undergo artificial hibernation in the hope of lessening permanent cerebral damage.[12] We believe that prolonged coma carries even more dangerous complications. Questions relating to minimal lethal doses, fatal concentrations of drugs in the blood, and effectiveness of therapy are uncertain. In acute poisoning, the uncertainty of factors such as: exact dosage, date of ingested or absorbed drugs, elapsed time before treatment, underlying physical state, and individual tolerance to drugs, makes it difficult if not impossible to foretell whether or not the patient will survive with or without a particular therapeutic procedure.

Megimide[13] is especially useful to unmask light cases of poisoning, but it is probably useless when massive doses of sedatives have been taken. Megimide stimulates respiratory and circulatory centers and restores reflexes and consciousness in light cases of sedative intoxication. However, an overdose of Megimide produces exaggerated reflexes, muscular twitching, tremor, clonus, and hyperventilation and epileptic potentials in the electroencephalogram. It is not a specific antidote against either barbiturate or glutethimide, such as Nalline hydrochloride* is against morphine. Megimide is given intravenously intermittently in doses of 50 mg. from every three to five minutes until muscle tone and pharyngeal and laryngeal reflexes have returned. An overdosage of Megimide may result in convulsions.

Some drugs are bound to proteins in the blood stream or even to proteins in the cells. It might be expected that the portion of drugs that is bound to plasma proteins cannot be removed by dialysis.[14] Berman, Jeghers, Schreiner, and Pallotta[1] observed no significant difference after dialysis in the concentration of pentobarbital sodium in plasma as compared with concentrations of the same drug in saline solution after dialysis. Even if the amount of a drug removed by hemodialysis is small, it may critically reduce the concentration of sedative from a fatal amount.

**Nalline hydrochloride (nalorphine hydrochloride: N-allyl-normorphine hydrochloride), Merck Sharp & Dohme.*

In one of our patients (case 2), no drugs were detected in the blood at the end of the second dialysis. Death probably was indirectly caused by drug poisoning, in that initial anoxic cerebral damage and complicating bronchopneumonia made the condition irreversible.

A patient with glutethimide poisoning may undergo remarkable alternation of presence and absence of symptoms within short intervals. He may be completely comatose and areflexic at one moment and at the next moment respond to painful stimuli. This alternation has been thought to be due to resorption from the small intestine of the glutethimide that is intermittently excreted in the bile.[2]

Summary

Four patients with severe glutethimide or barbiturate poisoning were treated with hemodialysis by the twin-coil artificial kidney. Three of the four patients survived: one died perhaps because the initial deep coma led to anoxic cerebral damage and was later complicated by bronchopneumonia.

Early dialysis may prevent clinical deterioration to an irreversible state, and may prevent the occurrence of complications. Dialysis can remove critical amounts of toxic substances from the blood, and reduce fatal concentrations in the blood to within the range of normal sedative concentration.

Addendum

Since we submitted this paper, we have successfully treated two more patients with acute barbiturate poisoning, using the artificial kidney.

References

1. Berman, L.B.; Jeghers, H. J.; Schreiner, G. E., and Pallotta, A. J.: Hemodialysis, effective therapy for acute barbiturate poisoning. J. A. M. A. **161**: 820-827, 1956.

2. Schreiner, G. E.; Berman, L. B.; Kovach, R., and Bloomer, H. A.: Acute glutethimide (Doriden) poisoning; use of bemegride (Megimide) and hemodialysis. A.M.A. Arch. Int. Med. **101**: 899-911, 1958.

3. Schreiner, G. E.: Role of hemodialysis (artificial kidney) in acute poisoning. A.M.A. Arch. Int. Med. **102**: 896-913, 1958.

4. McBay, A. J., and Katsas, G. G.: Glutethimide poisoning; report of four fatal cases. New England J. Med. **257**: 97-100, 1957.

5. Kolff, W. J.; Nakamoto, S., and Humphrey, D. C.: Recovery from anuria after suffocation in nitrogen—treatment with artificial kidney. Ohio State M. J. **55**: 1230-1232, 1959.

6. Kolff, W. J., and Watschinger, B.: Further development of coil kidney; disposable artificial kidney. J. Lab. & Clin. Med. **47**: 969-977, 1956.

7. Kolff, W. J.; Watschinger, B., and Vertes, V.: Results in patients treated with coil kidney (disposable dialyzing unit). J. A. M. A. **161**: 1433-1437, 1956.

8. Nakamoto, S., and Holmes, J. H.: Our experience in regional heparinization. Trans. Am. Soc. Art. Int. Org. **4:** 36-45, 1958.

9. Goldbaum, L. R.: Determination of barbiturates: ultraviolet spectrophotometric method with differentiation of several barbiturates. Analyt. Chem. **24:** 1604-1607, 1952.

10. Goldbaum, L. R.; Williams, M., and Koppanyi, T.: Determination of Doriden. Fed. Proc. **16:** 300, 1957.

11. Aoyama, S., and Kolff, W. J.: Treatment of renal failure with disposable artificial kidney; results in fifty-two patients. Am. J. Med. **23:** 565-578, 1957.

12. Kolff, W. J.: Artificial hibernation; technic, and observations on seriously ill patients. Cleveland Clin. Quart. **22:** 109-123, 1955.

13. Shaw, F. H.: Further experiences with "megimide"—barbiturate antagonist. M. J. Australia **2:** 889-891, 1955.

14. Sunshine, I., and Leonards, J. R.: Use of artificial kidney for removal of barbiturates in dogs. Proc. Soc. Exper. Biol. & Med. **86:** 638-641, 1954.

MANAGEMENT OF "INTRACTABLE" ASCITES IN DECOMPENSATED CIRRHOSIS

Favorable Response of Five Patients to Medical Treatment

CHARLES H. BROWN, M.D., MAURO MERLO, M.D.,*
Department of Gastroenterology
and
RICHARD C. BRITTON, M.D.
Department of Vascular Surgery

TRADITIONAL management of a patient with cirrhosis of the liver and associated ascites comprises a high-protein diet with supplemental vitamins and repeated paracenteses when the extent of ascites interferes with respiration, appetite, or comfort. Paracentesis has been given undue credit as a therapeutic measure, inasmuch as improvement in the patient usually has resulted from improved nutrition and hepatocellular function. Repeated paracenteses leach out the patient's plasma protein by plasmapheresis and actually are harmful. A most pitiful patient is the one with so-called intractable ascites, whose course involves progressive muscular wasting and cachexia as the ascites reaccumulates more rapidly after each paracentesis until the onset of jaundice, hepatic coma, hemorrhage from esophageal varices, and finally death.

We believe that too much reliance has been placed on repeated paracenteses as the only treatment for the cirrhotic patient with ascites, and that too little emphasis has been placed on the strict medical treatment. It is not sufficient simply to hand the patient a diet sheet outlining a high-protein and high-caloric intake. The responsible physician must see to it that the patient follows the prescribed diet. It is too easy to think: "This patient has intractable ascites and all we can do is to tap him repeatedly." Strict attention to minute details of medical management of the patient, although tedious, will usually cause a favorable response to treatment.

We shall discuss in this report the treatment of intractable ascites caused by decompensated cirrhosis, and the favorable response to it of five patients referred to us because of the apparently irreversible ascites.

Medical Treatment

The medical treatment of the patient with decompensated cirrhosis and ascites can be outlined as follows. All patients were admitted to the hospital and were given bed rest, and a diet consisting of 120 gm. of protein, 370 gm. of carbohydrate, and from 120 to 170 gm. of fat with no more than 500 mg. of salt daily. Diet diaries were kept of the exact caloric intake. The inclusion of fat in the diet

*Fellow in the Department of General Medicine.

8. Nakamoto, S., and Holmes, J. H.: Our experience in regional heparinization. Trans. Am. Soc. Art. Int. Org. **4:** 36-45, 1958.

9. Goldbaum, L. R.: Determination of barbiturates: ultraviolet spectrophotometric method with differentiation of several barbiturates. Analyt. Chem. **24:** 1604-1607, 1952.

10. Goldbaum, L. R.; Williams, M., and Koppanyi, T.: Determination of Doriden. Fed. Proc. **16:** 300, 1957.

11. Aoyama, S., and Kolff, W. J.: Treatment of renal failure with disposable artificial kidney; results in fifty-two patients. Am. J. Med. **23:** 565-578, 1957.

12. Kolff, W. J.: Artificial hibernation; technic, and observations on seriously ill patients. Cleveland Clin. Quart. **22:** 109-123, 1955.

13. Shaw, F. H.: Further experiences with "megimide"—barbiturate antagonist. M. J. Australia **2:** 889-891, 1955.

14. Sunshine, I., and Leonards, J. R.: Use of artificial kidney for removal of barbiturates in dogs. Proc. Soc. Exper. Biol. & Med. **86:** 638-641, 1954.

MANAGEMENT OF "INTRACTABLE" ASCITES IN DECOMPENSATED CIRRHOSIS

Favorable Response of Five Patients to Medical Treatment

CHARLES H. BROWN, M.D., MAURO MERLO, M.D.,*
Department of Gastroenterology
and
RICHARD C. BRITTON, M.D.
Department of Vascular Surgery

TRADITIONAL management of a patient with cirrhosis of the liver and associated ascites comprises a high-protein diet with supplemental vitamins and repeated paracenteses when the extent of ascites interferes with respiration, appetite, or comfort. Paracentesis has been given undue credit as a therapeutic measure, inasmuch as improvement in the patient usually has resulted from improved nutrition and hepatocellular function. Repeated paracenteses leach out the patient's plasma protein by plasmapheresis and actually are harmful. A most pitiful patient is the one with so-called intractable ascites, whose course involves progressive muscular wasting and cachexia as the ascites reaccumulates more rapidly after each paracentesis until the onset of jaundice, hepatic coma, hemorrhage from esophageal varices, and finally death.

We believe that too much reliance has been placed on repeated paracenteses as the only treatment for the cirrhotic patient with ascites, and that too little emphasis has been placed on the strict medical treatment. It is not sufficient simply to hand the patient a diet sheet outlining a high-protein and high-caloric intake. The responsible physician must see to it that the patient follows the prescribed diet. It is too easy to think: "This patient has intractable ascites and all we can do is to tap him repeatedly." Strict attention to minute details of medical management of the patient, although tedious, will usually cause a favorable response to treatment.

We shall discuss in this report the treatment of intractable ascites caused by decompensated cirrhosis, and the favorable response to it of five patients referred to us because of the apparently irreversible ascites.

Medical Treatment

The medical treatment of the patient with decompensated cirrhosis and ascites can be outlined as follows. All patients were admitted to the hospital and were given bed rest, and a diet consisting of 120 gm. of protein, 370 gm. of carbohydrate, and from 120 to 170 gm. of fat with no more than 500 mg. of salt daily. Diet diaries were kept of the exact caloric intake. The inclusion of fat in the diet

*Fellow in the Department of General Medicine.

was considered essential for palatability and for supplying fat-soluble vitamins. Supplemental feedings of a salt-poor protein powder* two hours after meals were given. Although probably not essential for those patients receiving a high-protein diet, lipotrophic agents† were given orally. Multiple vitamins with an emphasis on the vitamin-B complex, vitamin B-12, and crude liver extract were administered parenterally; vitamin K was administered to those patients in whom there was a prolonged prothrombin time.

Testosterone propionate (100 mg. intramuscularly once or twice a week) was given for its anabolic effect. Twenty-four-hour urine collections were obtained to determine the gross concentrations of sodium excretion; mercurial diuretics were usually withheld if less than 1 mEq. per liter of sodium was excreted. Later, with increased sodium excretion, from 1 to 4 ml. of a mercurial diuretic was given daily.

When signs of pre-coma, hepatic coma developed, or the amount of blood ammonia increased, treatment was given for ammonia or protein intoxication as previously outlined by Owens, Brown, and Britton.[1]

Rigid avoidance of alcohol was advised. Our five patients had been alcoholics, and strictly avoided further alcoholic intake. Although small amounts of alcohol may be harmless, it is difficult for these patients to limit alcoholic intake to a small amount; consequently, strict abstinence is strongly urged. Carbonic-anhydrase diuretics and ammonium salts were avoided, as they may precipitate hepatic coma.

There is considerable current interest in the role of the portacaval shunt operation for controlling ascites that is truly refractory to medical treatment. Ligation of the hepatic artery[2,3] and bilateral adrenalectomy[4] have also been recommended, but because of the high mortality rate and the difficulty of postoperative management, these procedures are not popular and we consider them contraindicated.

Case Reports

Case 1. A 46-year-old man, an engineer, was admitted to the Cleveland Clinic Hospital on April 4, 1959, because of loss of appetite and 40 pounds in weight during the six months prior to admission. Jaundice and abdominal swelling had been present for one month. A heavy drinker most of his adult life, he consumed about one fifth of whisky daily. Physical examination revealed the patient to be undernourished. Slight icterus of the sclerae and numerous spider nevi on the chest were present. There was pitting edema of the pretibial areas. The abdomen was distended and a fluid wave was palpable. The liver was enlarged, extending 12 cm. below the right costal margin. The spleen was palpable. Roentgenograms gave evidence of normal esophagus, stomach, duodenum, and colon. Abdominal paracentesis was performed for diagnostic purposes and 100 ml. of fluid was obtained. The result of the microscopic examination of the sediment was negative for neoplastic cells.

* *Protinal powder, The National Drug Company; or, Gevral protein, Lederle Laboratories.*

† *Choline dihydrogen citrate, 10 gr. t.i.d.*

During the six weeks in the hospital, the patient was treated with a strict hepatic program. His general condition improved greatly, and the icterus and ascites gradually subsided. At the time of discharge on June 2, 1959, he was advised to continue the program. When last examined on September 16, 1959, he was feeling well, his appetite had increased, and he had gained 17 pounds. No evidence of peripheral edema or ascites remained. The liver and spleen were still palpable under the costal margin but were greatly reduced in size. His clinical improvement was substantiated by laboratory tests showing an increase in the serum albumin from 1.9 to 3.8 gm. per 100 ml. The laboratory data are summarized in *Table 1*.

Table 1.—*Summary of data in case 1—ascites and decompensated hepatic cirrhosis before and after treatment*

Test	1959			
	April 16 (Before treatment)	June 2	June 30	Sept. 16
Hemoglobin, gm./100 ml.	11.4	11.6	11.6	13.3
Bilirubin, mg./100 ml.:				
Direct	2.9	1.7	—	0.4
Indirect	3.6	1.8	—	0.5
Serum albumin, gm./100 ml.	1.9	3.1	3.5	3.8
Serum globulin, gm./100 ml.	6.4	4.1	2.8	3.4
Prothrombin time, percentage of normal control	62%	80%	80%	80%
Bromsulphalein retention in 45 min., per cent	26%	22%	14%	12%
Cephalin-cholesterol flocculation, grade	3+	—	0	—
Thymol turbidity, units	9.3	—	2.6	1.3
Alkaline phosphatase, units	5.7	3.2	2.4	—
Serum transaminase, S. G. O.	60	30	20	30
Ascites, grade	4+	0	0	0
Edema, grade	2+	0	0	0
Weight, pounds	130	—	—	147

Comment. This patient with decompensated cirrhosis, ascites, and peripheral edema responded to medical treatment without paracenteses except for the removal of 100 ml. of ascitic fluid for diagnostic purposes. With improvement in nutrition and increase in albumin, spontaneous diuresis and disappearance of ascites occurred. In spite of the loss of edema and ascites, the patient gained 17 pounds.

Case 2. A 48-year-old man, a truck driver, was admitted to the Cleveland Clinic Hospital on September 7, 1958, because of progressive edema of the ankle for one year, and general weakness, loss of appetite, and increasing abdominal distention for two months. Ten days prior to admission, an abdominal paracentesis was performed at another hospital. An indwelling catheter had been inserted into the right lower quadrant of the abdomen, and approximately 20 liters of ascitic fluid was removed. For 15 years prior to admission the patient's alcoholic intake had been excessive.

On physical examination, numerous spider angiomas were observed on the chest. The abdomen was distended, and a fluid wave was demonstrated. Dilated veins were present in the abdominal wall. The liver was enlarged, extending 6 cm. below the right costal margin. Cytologic examination of the ascitic fluid showed absence of neoplastic cells. The indwelling abdominal catheter was removed. Needle biopsy of the liver was performed and the pathologic report stated that the hepatic architecture was greatly distorted by fibrous tissue with a large number of proliferated bile ducts. The pathologic diagnosis was portal cirrhosis.

Roentgenograms showed evidence of normal chest, esophagus, and stomach, and no evidence of esophageal varices. The patient was given medical treatment only, and was discharged from the hospital on September 25, 1958. He was free of ascites and edema of the ankle when examined one month later (October 24). He was advised to continue the medical treatment and to return at bimonthly intervals for progress studies.

The patient was readmitted to the hospital on May 14, 1959. An acute upper respiratory infection in the patient four weeks previously had been followed by dyspnea, edema, and increasing size of the abdomen. Physical examination showed evidence of a right pleural effusion as well as ascites. Thoracentesis was performed twice, and 2,500 ml. and 1,700 ml., respectively, of clear fluid were removed. Cytologic study of the fluids was negative for neoplastic cells. The patient improved on medical treatment and was discharged from the hospital on May 22 with the advice to follow the same hepatic program. He was examined in July, August, and December, 1959, for progress studies. The ascites and edema gradually disappeared. *(Fig. 1, A and B.)* The laboratory data are summarized in *Table 2.*

Comment. This patient was considered as having intractable ascites: 20 liters of ascitic fluid were removed in the course of 10 days. He responded to medical treatment, but again, eight months later, ascites, peripheral edema, and pleural effusion on the right side developed. He again responded to medical treatment. An indwelling catheter in the abdomen had been ineffective; whereas, strict medical treatment was effective in controlling the ascites.

Case 3. A 47-year-old man, an executive, was admitted to the Cleveland Clinic Hospital on October 29, 1955, because of progressive abdominal swelling, peripheral edema, weight-loss of 30 pounds, and severe generalized malaise of three months' duration. A heavy drinker most of his life, he consumed a pint of whisky daily. In the previous month he had undergone five paracenteses in another hospital, with the removal of 42 liters of ascitic fluid.

On physical examination the patient appeared emaciated, with a loss of muscular tissue of the chest and shoulders, and pitting edema of the legs, scrotum, and presacral

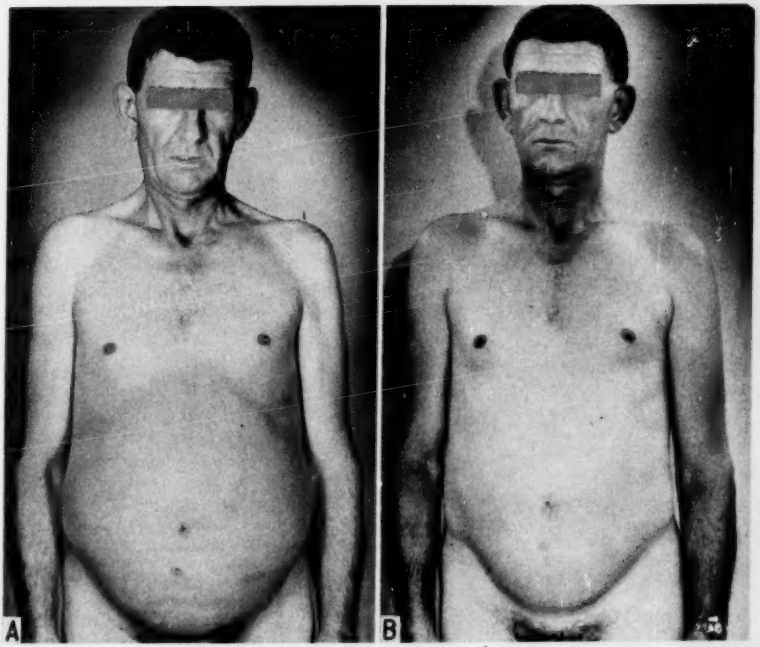

Fig. 1. Case 2. A, September, 1958, before treatment. Note protuberant abdomen and ascites; the umbilicus shifted position and is nearer the symphysis pubis than the xyphoid. This shift in position is characteristic in the cirrhotic patient with ascites, and is evident also in *Figures 2, 3,* and *4.* B, December, 1959, (20 months after treatment). Nutrition has improved and there is increased musculature. Ascites disappeared and did not recur and the patient gained 34 pounds.

area. Palmar erythema, icterus of the sclerae, and spider angiomas on the shoulder were present. The abdomen was distended and a fluid wave was demonstrated. The liver was enlarged, hard, nodular, and extended 5 cm. below the right costal margin. The spleen was not palpable. Dilated veins in the abdominal wall were prominently visible. A roentgenogram of the esophagus showed evidence of esophageal varices. During his stay in the hospital, two paracenteses were performed; 7.4 liters and 13.9 liters of fluid, respectively, were removed to relieve the respiratory distress. The result of the cytologic examination of the sediment was negative for neoplastic cells. The patient was treated with a strict hepatic program and was discharged on November 18, 1955.

He was readmitted to the hospital for progress hepatic studies in August, 1956, and in January and July, 1957. During those two years he followed the dietary program

Table 2.—*Summary of data in case 2—ascites and decompensated hepatic cirrhosis before and after treatment*

Test	1958		1959			
	Sept. (Before treatment)	Dec.	May	July	Aug.	Dec.
Hemoglobin, gm./100 ml.	14.6	—	12.9	—	15.5	15.8
Serum albumin, gm./100 ml.	1.0	2.5	1.82	3.01	2.32	4.16
Serum globulin, gm./100 ml.	5.2	4.2	4.69	3.64	3.71	2.66
Prothrombin time, percentage of normal control	80%	86%	50%	68%	68%	68%
Cephalin-cholesterol flocculation, grade	4+	4+	4+	3+	—	—
Thymol turbidity, units	3.2	—	7.5	—	—	—
Ascites, grade	4+	0	4+	2+	0	0
Edema, grade	2+	0	4+	2+	0	0
Weight, pounds	163-171	182	202-177	192	188	—

muscular strength. He did not require paracentesis, and when he was last examined there was no evidence of ascitic fluid. The liver was still palpable three fingerbreadths under the right costal margin, and the spleen also was palpable. *(Fig. 2, A, B, and C.)* The laboratory data are summarized in *Table 3.*

Comment. This patient had massive ascites: 63 liters of ascitic fluid were removed in the course of six weeks. He responded to medical treatment, had no recurrence of the ascites, gained in muscular strength and tone, and in nutrition. His clinical status improved to the extent that we were considering advising a portacaval shunt, when he suddenly suffered a fatal massive gastrointestinal hemorrhage at home.

Case 4. A 51-year-old unemployed man was first admitted to the Cleveland Clinic Hospital on June 2, 1958, because of ascites and peripheral edema of one and one-half years' duration. He had been treated at another hospital with a low-salt and high-protein diet, multivitamins, and oral diuretics. Response to this treatment had been poor, and he had required monthly paracentesis. Two months prior to admission, two Cooney buttons had been inserted in the lower abdominal wall in an attempt to drain the ascitic fluid. These did not function well. The patient was accustomed to a heavy alcoholic intake most of his adult life, and consumed about one pint of whisky daily.

Physical examination revealed an emaciated man who appeared to be chronically ill. Multiple spider angiomas were on the shoulders and arms, and there was palmar erythema. The abdomen was distended and a fluid wave was palpable; two plastic valves were present in both hypogastric areas. The liver and the spleen were not

palpable. Esophagoscopy revealed a small varix at the cardia. A roentgenogram of the chest showed evidence suggestive of a small amount of fluid in the right costophrenic angle.

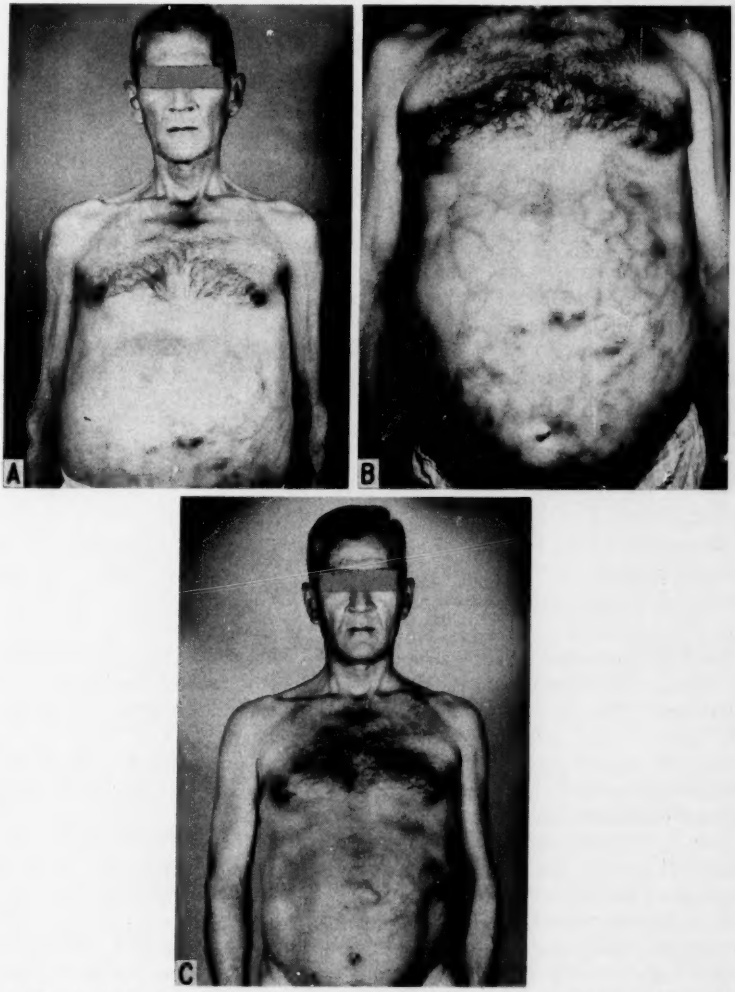

Fig. 2. Case 3. A, October, 1955, showing severe emaciation, loss of musculature, and ascites. B, Infrared photograph showing notable collateral circulation in the abdominal wall. C, January, 1957, showing a gain of 14 pounds in weight (despite loss of ascitic fluid), increased musculature, and improved nutrition.

Table 3.—*Summary of data in case 3—ascites and decompensated hepatic cirrhosis before and after treatment*

Test	1955	1956	1957	
	Nov. (Before treatment)	Aug.	Jan.	July
Hemoglobin, gm./100 ml.	13.4	12.4	13.5	14.5
Bilirubin, mg./100 ml.:				
Direct	0.7	0.6	0.9	1.1
Indirect	2.22	1.46	1.5	2.0
Serum albumin, gm./100 ml.	1.2	1.0	2.45	2.19
Serum globulin, gm./100 ml.	6.2	5.6	5.75	5.80
Prothrombin time, percentage of normal control	54%	72%	62%	58%
Bromsulphalein retention in 45 min., per cent	—	32%	—	38%
Cephalin-cholesterol flocculation, grade	4+	4+	4+	—
Thymol turbidity, units	23	17.5	19	17.5
Alkaline phosphatase, units	6.6	—	8.7	7.0
Ascites, grade	4+	?	0	0
Edema, grade	2+	0	0	0
Weight, pounds	191	197	205	205

On June 6, a specimen from a needle biopsy of the liver showed severe portal fibrosis, and proliferation of the bile ducts. There was chronic inflammatory infiltration of the portal areas. On June 11, under local anesthesia, the Cooney buttons were removed and 7 liters of ascitic fluid was withdrawn from the abdominal cavity. The patient was treated with a strict hepatic program that included mercurial diuretics. He showed a prompt and distinct clinical improvement and was discharged on June 28, 1958, with the recommendation that he continue the same program.

Subsequent examinations have shown his progress to be satisfactory, and except for occasional pain in the lower abdomen, he has felt well. In August, 1958, one paracentesis was performed and 6.3 liters of ascitic fluid was removed. He was last examined in December, 1959, and had had no recurrence of ascites or retention of fluid. The patient had gained 25 pounds in weight, had a good appetite, was working regularly, and felt well. *(Fig. 3, A, B, and C.)* The laboratory data are summarized in *Table 4.*

Comment. This patient had intractable ascites for one and one-half years and had been unable to work. Repeated paracenteses were necessary, and as a last resort, (in another hospital) two Cooney buttons had been placed in the abdominal wall in an

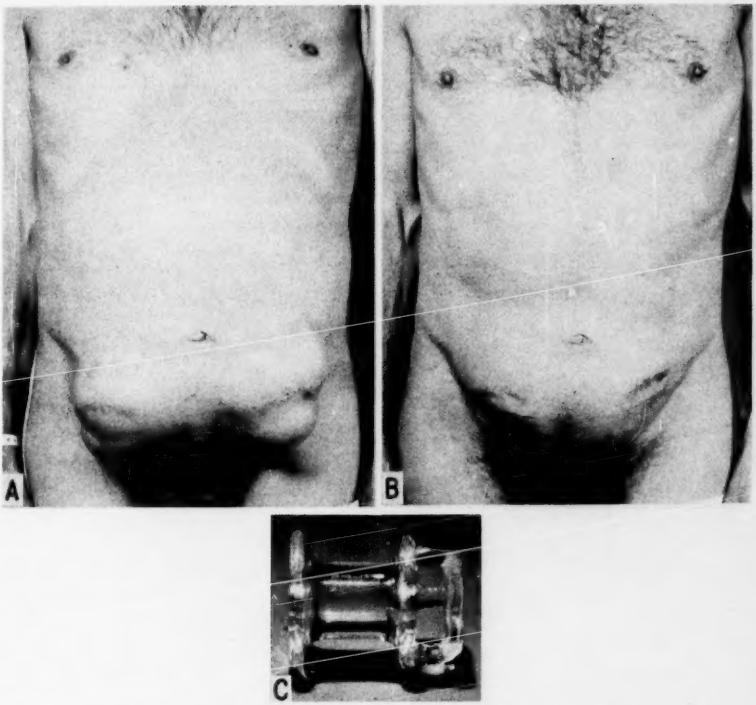

Fig. 3. Case 4. A, June, 1958, showing ascites and bulging in both lower quadrants caused by two Cooney buttons inserted two months previously (in another institution) in an attempt to control the ascites. The Cooney buttons did not function, and caused pain. B, January, 1959, six months after A. No ascites was present, although the patient had gained 13 pounds. C, One of the Cooney buttons that were removed.

attempt to drain the ascitic fluid. The patient responded satisfactorily to strict medical therapy advised by us, and the Cooney buttons were removed. He has had no ascites, has required no paracenteses in the past 16 months, and was able to return to work.

Case 5. A 51-year-old man, a laborer, first entered the Cleveland Clinic Hospital on April 4, 1958, because of jaundice and ascites of two months' duration. He had been treated in another hospital and had had five paracenteses; 8 liters of fluid was removed each time. He had been a heavy drinker for 15 years, consuming about one-half pint of whisky and two or three pints of beer daily.

On physical examination he appeared undernourished. Several spider nevi were on the anterior chest. The abdomen protruded and a fluid wave was palpable. The spleen and liver were not palpable. Pitting edema of the legs was present. Roentgenograms gave evidence of normal chest, esophagus, stomach, and duodenum. On April 19, an

Table 4.—*Summary of data in case 4—ascites and decompensated hepatic cirrhosis before and after treatment*

Test	1958			1959	
	June (Before treatment)	Sept.	Nov.	Jan.	Dec.
Hemoglobin, gm./100 ml.	13.7	14.4	14.4	14.2	—
Bilirubin, mg./100 ml.:					
Direct	0.2	0.4	0.1	—	—
Indirect	0.6	0.7	1.0	—	—
Serum albumin, gm./100 ml.	2.4	2.4	2.7	3.0	—
Serum globulin, gm./100 ml.	3.5	5.1	3.8	3.0	—
Prothrombin time, percentage of normal control	100%	—	—	100%	—
Bromsulphalein retention in 45 min., per cent	29%	24%	23%	21%	—
Cephalin-cholesterol flocculation, grade	3+	—	—	—	—
Thymol turbidity, units	4	—	—	—	—
Alkaline phosphatase, units	8.5	—	—	—	—
Ascites, grade	4+	0	0	0	0
Edema, grade	4+	0	0	0	0
Weight, pounds	160	155	168	171	180

abdominal paracentesis was performed and 6 liters of cloudy fluid was removed. The result of the microscopic examination of the sediment was negative for neoplastic cells. Five days later a specimen of a needle biopsy of the liver showed an irregular nodulation and broad zones of dense fibrous tissue containing numerous small bile ducts. The pathologic diagnosis was inactive postnecrotic cirrhosis.

The patient was treated with a strict hepatic program for 10 days and was discharged from the hospital on May 3. He was advised to continue with the same program, and to report periodically. His progress has been excellent up to December, 1959, when he was last examined. His appetite has been good and he has gained 34 pounds in weight. There has never been evidence of a recurrence of ascites or of peripheral edema. *(Fig. 4, A and B.)* The laboratory data are summarized in *Table 5.*

Comment. This patient had decompensated cirrhosis with intractable ascites, and had had 46 liters of ascitic fluid removed by paracenteses. After institution of strict medical therapy, no further paracenteses have been necessary in the 20 months of treatment. There have been improvement in the amount of serum albumin, in general nutrition, in muscle tone, and an increase in weight.

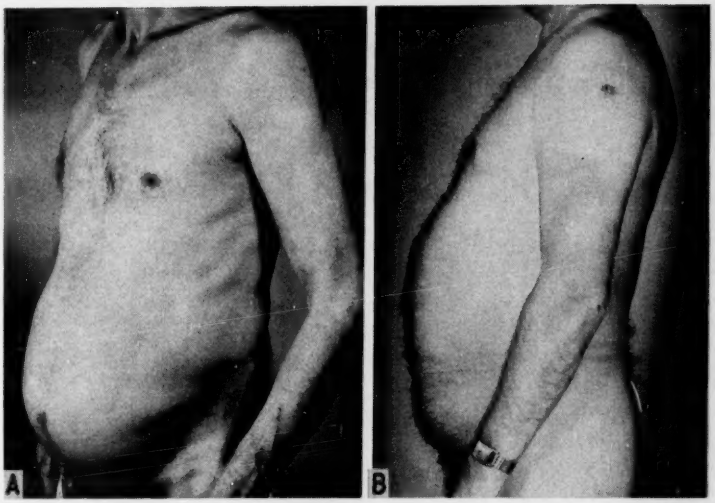

Fig. 4. Case 5. A, April, 1958, before treatment; note muscular wasting of neck, shoulders and arms, and great distention of the abdomen with ascites. B, September, 1959, improvement is evidenced by increased musculature, by the absence of ascites, and a gain of 25 pounds in weight despite the loss of ascitic fluid.

Discussion

Ascites is one of the most prominent and frequent physical signs in the decompensated stage of cirrhosis. The pathogenesis of ascites and edema in the cirrhotic patient is dependent upon factors that include: severity of portal hypertension, state of increased capillary permeability, presence of hypoproteinemia and hypoalbuminemia, retention of sodium, secondary aldosteronism, the stage of hepatic disease, and the type, extent, and cause of obstruction of outflow of hepatic blood. The factors that contribute to the formation and recurrence of ascites recently have come under close scrutiny. As a result, great emphasis is being placed upon the roles of the total body sodium, the type and extent of obstruction of hepatic blood flow, the stage of the hepatic disease, and secondary aldosteronism.

The increasing emphasis upon the importance of the role of sodium in the production and maintenance of ascites is based upon the demonstration that patients with decompensated cirrhosis retain sodium and excrete meager amounts, particularly during active formation of ascites. Farnsworth,[5] and Ricketts, Eichelberger, and Kirsner[6] noted that sodium was almost absent from the urine, and Eisenmenger, Blondheim, Bongiovanni, and Kunkel[7] noted that the sodium content was low in the sweat and saliva of patients who are forming ascites.

Table 5.—*Summary of data in case 5—ascites and decompensated hepatic cirrhosis before and after treatment*

Test	1958		1959				
	April (Before treatment)	July	Jan.	April	July	Sept.	Dec.
Hemoglobin, gm./100 ml.	13.7	16.4	17.8	—	18.4	17.4	16.6
Bilirubin, gm./100 ml.:							
Direct	0.1	0.1	0.1	—	0.6	—	—
Indirect	0.9	0.7	0.5	—	0.4	—	—
Serum albumin, gm./100 ml.	1.7	3.0	3.5	4.3	4.4	4.16	4.94
Serum globulin, gm./100 ml.	3.5	4.1	3.4	3.1	2.9	2.32	2.31
Prothrombin time, percentage of normal control	80%	100%	—	—	—	—	—
Bromsulphalein retention in 45 min., per cent	40%	24%	20%	10%	—	23%	14%
Cephalin-cholesterol flocculation, grade	2+	Neg.	Neg.	—	1+	—	—
Thymol turbidity, units	6	4.1	2.1	—	1.9	—	—
Ascites, grade	4+	0	0	0	0	0	0
Edema, grade	4+	0	0	0	0	0	0
Weight, pounds	157-124	151	165	158	157	158	155½

The electrolyte pattern in patients with cirrhosis and ascites is similar to that seen in hyperaldosteronism, and it has been demonstrated that many cirrhotic patients with ascites excrete abnormally large amounts of aldosterone in the urine.[4,8,9] Consequently, it has been postulated that secondary hyperaldosteronism may be a factor in the development of ascites in cirrhotic patients. Kerr, Read, Haslam, and Sherlock[10] administered an aldosterone antagonist (spirolactone*) to four patients with cirrhosis and intractable ascites, and diuresis of both sodium and water ensued in three of them. On an experimental basis, similar good results from the use of aldosterone antagonists in patients with intractable ascites have been reported by others, although undesirable side-effects have been the loss of appetite, nausea, and vomiting. The use of aldosterone antagonists and spirolactone in the treatment of the decompensated cirrhotic patient with ascites is still experimental, and not yet a part of standard treatment for these patients.

Salt restriction in the past has been inadequately controlled in the patient with decompensated cirrhosis. The so-called low-sodium diets have actually represented a sodium overload for patients with ascites. Restriction of sodium to 500 mg. or less daily is necessary.

* *Aldactone, G. D. Searle & Co.*

During the period in which the patient is actively accumulating ascites he may be refractory to the action of diuretics. Forced diuresis may occur through use of the newer carbonic-anhydrase inhibitors, but this is usually a forced excretion of water and potassium without a corresponding excretion of sodium. Carbonic-anhydrase-inhibiting diuretics given to a patient with decompensated cirrhosis have precipitated hepatic coma. The mechanism by which such diuretics induce hepatic coma may be through lowering the concentration of plasma potassium, as Sherlock[11] reported. The carbonic-anhydrase-inhibiting diuretics, including chlorothiazide*, hydrochlorothiazide†, and acetazolamide‡, are contraindicated in these patients. If a diuretic is used in the patient with decompensated cirrhosis, mercurial diuretics with supplemental potassium chloride intake are preferable. Ammonium chloride, to enhance the diuretic action of the mercurial agent, is absolutely contraindicated, because of the possibility of causing ammonia intoxication and hepatic coma.

The patient with decompensated cirrhosis and ascites, limited to a 500-mg. salt intake daily, in addition to a high-protein diet and other measures, will frequently have no further increase in the ascites. After a period of stabilization lasting from several days to several months, spontaneous diuresis and disappearance of the ascites may occur. It is during stabilization of the ascites that a mercurial diuretic, by causing a diuresis of water and subsequently sodium, may be helpful. When diuresis occurs and ascites disappears, whether spontaneous or aided by mercurial diuretics, hepatic function tests usually indicate that a general improvement in hepatocellular function has also occurred.

The greatest criticism of the traditional management of ascites is the frequent paracenteses that result in a great loss of serum albumin with each tap, a loss of albumin ranging from 20 to 266 gm.[12,13] The high cost of salt-poor serum albumin to replace that lost during paracentesis is formidable, and the supply of free salt-poor albumin available through the Red Cross blood program is greatly limited. Ideally, the amount of serum albumin lost at each paracentesis should be determined, and this amount should be given intravenously, since the periodic loss of this potent osmotic factor can only serve to perpetuate the ascites.§ Paracentesis has been used by us only for the purpose of relieving severe discomfort, to improve the appetite, to rule out carcinomatosis by cytologic study, and in preparation for needle biopsy of the liver.[14] Seldom has more than one paracentesis,

Diuril (chorothiazide), Merck Sharp & Dohme.

†HydroDIURIL (hydrochlorothiazide), Merck Sharp & Dohme.

‡Diamox (acetazolamide), Lederle Laboratories.

§Recently in other patients, when paracentesis was necessary, because of the high cost of serum albumin, ascitic fluid was saved. This ascitic fluid subsequently was dialyzed in the artificial kidney to remove salt and water. The concentrated and salt-poor ascitic fluid was then returned to the patient intravenously to replace the albumin. This procedure has been done in six patients with apparently beneficial results. (R. C. Britton, and S. Nakamoto; see page 82 of this issue.)

usually for diagnostic purposes, been necessary. By such restriction of paracenteses and in association with rigid salt restriction, a high-protein, high-carbohydrate and high-caloric diet, suitable vitamins, and other measures, it has been possible to stabilize ascites without surgical intervention.

Summary

Five alcoholic patients had intractable ascites and decompensated cirrhosis. When first seen, four patients had had repeated paracenteses. One patient had had an indwelling catheter placed in the abdomen. In another patient two Cooney buttons had been placed in the abdominal wall. All of the patients responded to medical treatment, obtained relief of the ascites, and improved in general nutrition and in hepatic function. It may be questionable whether ascites caused by decompensated cirrhosis is ever intractable if medical treatment is strict, intensive, and prolonged.

Medical treatment of the cirrhotic patient with ascites is outlined. Repeated paracenteses, carbonic-anhydrase diuretics, and ammonium salts are avoided. Avoidance of alcohol is imperative. A 500-mg. sodium, high-protein, high-caloric diet with supplemental protein feedings between meals is used, and a careful diet diary is kept to determine the actual intake. Supplemental vitamins are administered orally and parenterally, and vitamin-B complex, liver extract, and depotestosterone are injected parenterally. Mercurial diuretics may be given, and serum albumin used when available. With perseverance and persistence on the part of both the patient and the physician, ascites in most cases of decompensated cirrhosis should respond to medical treatment.

References

1. Owens, F. J.; Brown, C. H.; Britton, R. C., and Faulkner, W. R.: Episodic hepatic encephalopathy: problem of all specialties. Cleveland Clin. Quart. **26:** 1-11, 1959.

2. Rienhoff, W. F., Jr., and Woods, A. C., Jr.: Ligation of hepatic and splenic arteries in treatment of cirrhosis with ascites. J.A.M.A. **152:** 687-690, 1953.

3. Berman, J. K.; Habegger, E. D., and Fields, D. C.: Arterial ligations in cirrhosis of liver; selection of patients and results. Connecticut M. J. **18:** 197-203, 1954.

4. Giuseffi, J.; Werk, E. E., Jr.; Larson, P. U.; Schiff, L., and Elliott, D. W.: Effect of bilateral adrenalectomy in patient with ascites and postnecrotic cirrhosis. New England J. Med. **257:** 796-803, 1957.

5. Farnsworth, E. B.: Electrolyte partition in patients with edema of various origins; sodium and chloride. Am. J. Med. **4:** 338-342, 1948.

6. Ricketts, W. E.; Eichelberger, L., and Kirsner, J. B.: Observations on alterations in electrolytes and fluid balance in patients with cirrhosis of liver with and without ascites. J. Clin. Invest. **30:** 1157-1170, 1951.

7. Eisenmenger, W. J.; Blondheim, S. H.; Bongiovanni, A. M., and Kunkel, H. G.: Electrolyte studies on patients with cirrhosis of liver. J. Clin. Invest. **29:** 1491-1499, 1950.

8. Chart, J. J., and Shipley, E. S.: (Abs.) Mechanism of sodium retention in cirrhosis of liver. J. Clin. Invest. **32:** 560, 1953.

9. Leutscher, J. A., Jr., and Johnson, B. B.: Observations on sodium-retaining corticoid (aldosterone) in urine of children and adults in relation to sodium balance and edema. J. Clin. Invest. **33:** 1441-1446, 1954.

10. Kerr, D. N.; Read, A. E.; Haslam, R. M., and Sherlock, S.: Use of steroidal spirolactone in treatment of ascites in hepatic cirrhosis. Lancet **2:** 1084-1087, 1958.

11. Sherlock, S.: Hepatic coma; presented at American Association for Study of Liver Disease, Chicago, Nov. 1959.

12. Berman, J. K., and Hull, J. E.: Experimental ascites—its production and control. Surgery **32:** 67-75, 1952.

13. Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts. Vol. 2. Philadelphia: Lea & Febiger, 1953, pp. 609-808; p. 702.

14. Brown, C. H.: Biopsy of liver with Vim-Silverman needles. Mississippi Valley M. J. **81:** 198-200, 1959.

INTRAVENOUS INFUSION OF DIALYZED, AUTOGENOUS, ASCITIC FLUID IN THE MANAGEMENT OF CIRRHOTIC ASCITES

A Preliminary Report of Favorable Results in Six Patients

RICHARD C. BRITTON, M.D.,
Department of Vascular Surgery
and
SATORU NAKAMOTO, M.D.,*
Department of Artificial Organs

IN recent years the traditional treatment of repeated paracenteses in the management of cirrhotic ascites has waned in favor of attempts to correct the underlying physiologic defects. The relative importance of abnormal renal tubular absorption of sodium, portal hypertension, abnormal osmoreceptor responses, secondary aldosteronism, and reduced protein oncotic pressure in the formation of cirrhotic ascites has been shown.[1-6] Sodium retention appears to be basic to the formation of ascites and, in many patients, strict salt restriction is sufficient to control ascites.[7-9] However, in patients with imminent or actual hemorrhage from esophageal varices, prolonged dietary measures are impractical and potentially dangerous. A reduced surgical mortality in patients free of ascites has been the impetus for seeking a safe rapid means of eliminating or controlling ascites.[10]

Repeated paracenteses reduce total body sodium, but also have the disadvantage of depleting plasma proteins. Infusion of ascitic fluid intravenously has been advocated in the past, but this amounts to a transfer of sodium and water from one extracellular space to another, and the volumes to be infused are prohibitive.[11-13]

Intravenous infusion of concentrated ascitic fluid without water and sodium and with conservation of proteins would be most desirable. This report describes a method of concentrating ascitic fluid and rendering it sodium poor. Such concentration is possible by ultrafiltration and dialysis. This technic has proved practical in nine dialyses of ascitic fluid from six cirrhotic patients. No serious reactions occurred, and ascites formation was arrested after single treatments in five patients, and after four treatments in one patient. Only each patient's own processed fluid was given to him intravenously.

Selection of Patients

All six patients, three men and three women, had postnecrotic cirrhosis as confirmed by liver biopsy studies. Five patients had large volumes of ascites for longer than three months; of these, three patients had had one or more paracenteses with rapid reaccumulation of ascites; the sixth patient had active hepatitis with

*Fellow in the Department of Artificial Organs.

hepatosplenomegaly, thrombosis of the portal vein, confirmed by splenoportography, and actively forming ascites. On a high-protein, high-caloric diet with sodium intake limited to 10 mEq. daily, each patient excreted less than 10 mEq. per liter of sodium in the urine, and gained from one to three pounds in body weight daily.

Technic

The procedure was uniform for each of the six cirrhotic patients. All measurements and analyses, such as of body weight, serum electrolytes, serum proteins, urinary volume and electrolytes, were made immediately before and after paracentesis and before and after infusion of the autogenous ascitic fluid. Ascitic fluid was analyzed for electrolytes, glucose, and osmolality. Samples were used for culture, paper electrophoresis, and cytologic study.

Paracentesis. Trocar paracentesis was performed in the operating room under aseptic conditions. Ascitic fluid was drained into 10-liter sterile plastic bags containing between 20 and 40 mg. of heparin-sodium to prevent clotting of fibrin. The bags were equipped with inflow and outflow tubes.

Dialysis and ultrafiltration. The inflow and outflow tubes on the plastic bag were attached to a twin-coil disposable artificial kidney* having a dialyzing surface of 18,000 sq. cm. Ultrafiltration pressures were manually controlled by a screw clamp on the outflow tube; pressures ranged from 280 to 300 mm. of Hg in the coils. An automatic device† controlled pressure to prevent rupture of the cellophane membranes in the coils.

The 50-l. dialyzing solution of the artificial kidney consisted of 15 per cent dextrose in water. The dextrose, as shown by Lenggenhager,[14] enters the ascitic fluid as sodium leaves it, and prevents the precipitation of protein. Duration of dialysis ranged between 4 and 10 hours, depending upon the volume of ascitic fluid to be processed. One change of the dialyzing solution reduced dialysis time in obtaining ascitic fluid sodium concentrations of less than 10 mEq. per liter. Tetracycline hydrochloride, 2 gm., was added to the rinsing fluid. The usual filters of the artificial kidney help to eliminate particulate matter. Immediately after dialysis and ultrafiltration, the concentrated, salt-poor fluid was stored in sterile 250-ml. containers at 5 C. for overnight.

Infusion. The day after dialysis and ultrafiltration, the treated ascitic fluid was intravenously infused in the patient. The fluid was viscous and was administered through 18-gauge needles. Plastic blood filters were connected in the tubing to collect all residual particulate material not eliminated by dialysis. Infusion time averaged 250 ml. per hour. During infusion and every four hours thereafter, blood pressure, pulse, respiration, and temperature were measured.

**Manufactured by Travenol Laboratory, Inc., Morton Grove, Illinois.*

†Mercoid Control, manufactured by Mercoid Corporation, Chicago, Illinois.

Results

Alterations in ascitic fluid. Tables 1 and *2* summarize the effects of dialysis and ultrafiltration on composition of ascitic fluid. The average reduction in sodium content to 5.8 mEq. per liter, and concentration of protein to five times that of the original ascitic fluid have resulted in a solution with a salt-poor albumin con-

Table 1.—*Quantitative alterations in ascitic fluid after dialysis and ultrafiltration*

(Average data; nine samples from six patients)

Determination	Before dialysis	After dialysis
Total volume, ml.	7000	750
Total protein, gm./100 ml.	1.6	8.3
Albumin, gm./100 ml.	(0.9)	(4.8)
Globulin, gm./100 ml.	(0.7)	(3.5)
Alpha-1	(0.05)	(0.30)
Alpha-2	(0.06)	(0.31)
Beta	(0.19)	(0.74)
Gamma	(0.52)	(2.12)
Sodium, mEq./l.	130.0	5.8
Potassium, mEq./l.	3.9	0.3
Chloride, mEq./l.	103.0	4.3
Glucose, mg./100 ml.	151.0	10044.0

Table 2.—*Quantitative sodium, water, and albumin exchange after dialysis of ascitic fluid*

(Nine samples from six patients)

Sample	Total sodium removed, mEq.	Total water removed, ml.	Total albumin returned, gm.
1	1071	7500	24.7
2	1081	7430	96.9
3	1536	10300	93.2
4	747	5350	28.6
5	1051	7800	35.7
6	739	5000	30.0
7	272	1700	23.8
8	750	5200	59.0
9	827	5400	17.1

tent approaching that supplied by the Red Cross, or that commercially available. Cultures were sterile before and after dialysis, except for one sample that grew *Staphylococcus albus* before, but not after, dialysis, and was thought to be a contaminant. Cytologic study showed the absence of neoplastic cells, except for one patient with cirrhosis and carcinomatosis whose pleural fluid contained neoplastic cells.

Reactions to infusion. Three patients had mild chills, and fever as high as 102 F., transient in nature, without further reaction during infusion. No significant alterations in serum electrolytes or low-sodium syndrome occurred. Diuresis and natruresis, mild and transient, occurred in all patients.

Clinical responses. Stabilization of ascites occurred in five patients, as shown by stable body weight and clinical examination. Portacaval shunts were performed one week later in two of these patients. The sixth patient regained 45 pounds of ascites the month after his first tap and infusion, 20 pounds in the month after the second infusion, 8 pounds 10 days after the third infusion; ascites has remained stable since the fourth infusion. He had been considered to have "intractable ascites" and required monthly paracentesis despite strict medical management. The ascites in the other five patients has remained stable for as long as four months of follow-up study. With improvement in hepatocellular function on an intensive medical program, increasing sodium excretion in the urine has permitted easing the restriction of sodium intake without recurrence of ascites.

Discussion

Infusion of ascitic fluid, autogenous and homologous, fresh, refrigerated, or lyophilized, had considerable use in the late 1930's, primarily as a substitute for blood in the treatment of shock, nephrosis, and hypoproteinemic states.[15-17] Few serious reactions were observed except with contaminated fluid or homologous fluid; anaphylaxis, fever, urticaria, and chills were reported. In certain clinics, suitably cross-matched ascitic fluid was used in homologous transfusion, while in others no attempt at matching was made, largely with impunity.[15] The ready availability of blood and blood derivatives made infusion of ascitic fluid unnecessary for these purposes.

In 1951, Emmrich and Fliege[18] reported good response to repeated infusion of untreated ascitic fluid in two patients, with fair results in a third patient. It is possible that the benefit obtained was largely due to the associated medical treatment, and to time, rather than to a direct effect upon retention of sodium and water.

The procedure of ultrafiltration and dialysis of ascitic fluid, and infusion intravenously, appears to be practical in removing excessive total body sodium and water without protein loss. Prolonged clinical benefit probably depends more upon improvement in hepatocellular function than in the transient physicochemical alterations that result from infusion of concentrated salt-poor ascitic fluid.

However, if surgical intervention is imperative, rapid preoperative *control* of ascites, is important if surgical mortality is to be lessened.

Summary

1. Controlled reduction of water and sodium content of ascitic fluid without protein loss can be achieved by ultrafiltration and dialysis in a twin-coil disposable artificial kidney.

2. Intravenous infusion of this autogenous, concentrated ascitic fluid appears to be a safe method of reducing excessive total body sodium without protein loss.

3. This technic has been useful in stabilizing ascites in six patients with postnecrotic cirrhosis.

References

1. Havens, W. P., Jr., and Bluemle, L. W., Jr.: Effect of human serum albumin and mercurial diuretics on ascites in patients with hepatic cirrhosis. Gastroenterology **16:** 455-465, 1950.

2. Werk, E. E., Jr., and others: Effect of bilateral adrenalectomy in patient with massive ascites and postnecrotic cirrhosis. Proc. Cent. Soc. Clin. Res., J. Lab. & Clin. Med. **48:** 958-959, 1956.

3. Hertz, R.; Pittman, J. A., and Graff, M. M.: Amphenone: toxicity and effects on adrenal and thyroid function in man. J. Clin. Endocrinol. **16:** 705-723, 1956.

4. Renold, A. E., and others: Inhibition of aldosterone secretion by amphenone in man. New England J. Med. **256:** 16-21, 1957.

5. Wolfe, S. J.; Fast, B.; Stormont, J. M., and Davidson, C. S.: Sodium diuresis from amphenone given to patients with cirrhosis and ascites. New England J. Med. **257:** 215-218, 1957.

6. Madden, J. L.; Lore, J. M., Jr.; Gerold, F. P., and Ravid, J. M.: Pathogenesis of ascites and consideration of its treatment. Surg. Gynec. & Obst. **99:** 385-391, 1954; correction, **99:** 782, 1954.

7. Goodyer, A. V. N.; Relman, A. S.; Lawrason, F. D., and Epstein, F. H.: Salt retention in cirrhosis of liver. J. Clin. Invest. **29:** 973-981, 1950.

8. Davis, J. O.; Howell, D. S., and Southworth, J. L.: Mechanisms of fluid and electrolyte retention in experimental preparations in dogs. III. Effect of adrenalectomy and subsequent desoxycorticosterone acetate administration on ascites formation. Circulation Res. **1:** 260-270, 1953.

9. Warner, G. F.; Sweet, N. J., and Dobson, E. L.: Sodium space and body sodium content, exchangeable with sodium^{24}, in normal individuals and patients with ascites. Circulation Res. **1:** 486-490, 1953.

10. Reemtsma, K.; Carlson, R. E.; Habif, D. V., and Barker, H.: Changes in sodium metabolism following portacaval shunts in patients with cirrhosis and ascites. S. Forum **7:** 422-425, 1957.

11. Patek, A. J., Jr., and others: Effects of intravenous injection of concentrated human serum albumin upon blood plasma, ascites, and renal functions in three patients with cirrhosis of liver. J. Clin. Invest. **27:** 135-144, 1948.

12. McKee, F. W.; Wilt, W. G., Jr.; Hyatt, R. E., and Whipple, G. H.: Circulation of ascitic fluid; interchange of plasma and ascitic fluid protein as studied by means of C^{14}-labeled lysine in dogs with constriction of vena cava. J. Exper. Med. **91:** 115-122, 1950.

13. McKee, F. W.; Yuile, C. L.; Lamson, B. G., and Whipple, G. H.: Albumin and globulin circulation in experimental ascites; relative rates of interchange between plasma and ascitic fluid studied with C^{14}-labeled proteins. J. Exper. Med. **95:** 161-172, 1952.

14. Lenggenhager, K.: Eine praktische Lösung des Blutersatzes. Zentralbl. Chir. **67:** 1961-1967, 1940.

15. Davis, H. A., and Blalock, J. F., Jr.: Autologous and homologous transfusion of ascitic fluid. J. Clin. Invest. **18:** 219-224, 1939.

16. Maes, U., and Davis, H. A.: Fluid replacement in surgical states, with particular reference to transfusion of ascitic fluid: clinical and experimental study. Arch. Surg. **42:** 453-479, 1941.

17. Molina, R. D.; Santos, H. A., and Alimurung, M. M.: Intravenous use of human ascitic fluid in shock, nephrosis and allied conditions. Am. J. M. Sc. **213:** 435-440, 1947.

18. Emmrich, R., and Fliege, H. J.: Die Aszites-Reinfusion als Therapie der dekompensierten Leberzirrhose. (Therapeutic ascites re-infusion in decompensated liver cirrhosis.) Med. Welt. **20:** 931-933, 1951.

MYELOMENINGOCELE, THE RESULT OF *RUPTURE* OF THE EMBRYONIC NEURAL TUBE

W. JAMES GARDNER, M.D.
Department of Neurological Surgery

The IV *stumbling blocks to truth:*
I. The influence of fragile or unworthy authority.
II. Custom.
III. The imperfection of the undisciplined senses.
IV. Concealment of ignorance by ostentation of seeming wisdom.

—Br. Roger Bacon, O.F.M.
(1214-1294 A.D.)

SINCE the days of Von Recklinghausen[1] it has been recognized that myeloschisis (an open portion of the neural tube) is the embryonic forerunner and basic lesion in the common form of myelomeningocele.[2] The closed portion of the neural tube, particularly above the myelomeningocele, is dilated (hydromyelia). In many infants, this dilatation of the central canal increases as it passes toward the lesion, and there is progressive attenuation first of the roof plate, then of the floor plate, until the cord bifurcates into two imperfect cords[3,4] (diastematomyelia) each with a dilated central canal. Each cord is rotated 90 degrees so that the anterior fissures face each other in the mid-line.[5] The dilated central canal of each cord as it enters the myelomeningocele opens onto a flat mass of neural tissue representing "an exposed unclosed neural plate divided in half down the midline."[6] Caudal to the myelomeningocele these two plates come together again to form a spinal cord.

Solely on the basis of appearance, it has been assumed that the open, everted neural tube of the myeloschisis represents a failure of the tube to close.[1,2] Morgagni,[7] however, believed that "these watery tumors of the vertebrae" represented a disruption resulting from the pressure of fluid "descending in the tube of the spine" from the hydrocephalic head. Von Recklinghausen[1] discredited Morgagni's hydromyelic theory. He refused to believe that hydrostatic pressure could accomplish such disruption, and because the neural tube was open, he asserted that it had failed to close.

Recently Patten,[8] in a study of three human embryos with myeloschisis, demonstrated local overgrowth of neural tissue at the site of the defect, and therefore concluded that this overgrowth had *prevented the tube from closing.* He maintained this view despite Fowler's[9] demonstration that similar overgrowth in the chick embryo occurs *after* slitting open the roof plate of a *closed* neural tube.

Therefore, to this day, because of custom and the influence of the great Von Recklinghausen's authority, the araphic theory has gone unchallenged, even though

embryologic, pathologic, clinical, and experimental evidence favors Morgagni's less fragile hypothesis. The purpose of this paper is to assemble this evidence and show that the open neural tube in myeloschisis is the result of *rupture* and not *failure to close.*

Embryologic Basis

The embryonic central nervous system originates as the ectodermal neural plate, which deepens into a groove and then fuses posteriorly to form a continuous closed cavity that constitutes primitive ventricles and central canal of the cord *(Fig. 1).* Closure of the tube begins in the cervical region on the twenty-first day

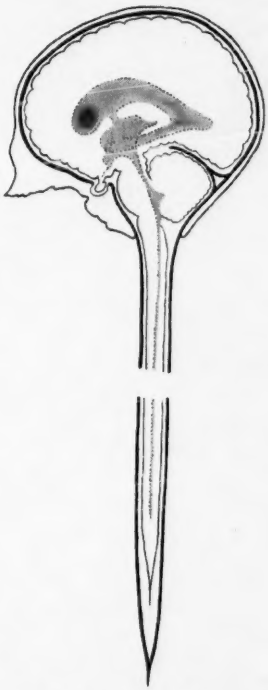

Fig. 1. Sketch showing the neural tube of a young embryo as it would appear if transposed to the mature nervous system. There is no outlet from the fourth ventricle and no subarachnoid space. The central canal is a long diverticulum of the fourth ventricle.

and progresses in zipper-like fashion both cranially and caudally. The cranial end closes on the twenty-fifth day, the caudal end on the twenty-ninth day. The slitlike lumen of this primitive spinal cord is bounded by thick lateral plates of

neural tissue and by thin roof and floor plates. The cord is bordered laterally by paired mesodermal somites, posteriorly by cutaneous ectoderm, anteriorly by mesodermal notochord, and beyond that by endoderm constituting primitive gut *(Fig. 2).* Weed[10] has shown that fluid forms in this closed cavity *before facilities are provided for its removal.* Because of this unusual chronologic sequence, the lumen undergoes rapid distention to constitute a degree of hydrocephalus *and hydromyelia* that is physiologic in embryonic life.[11]

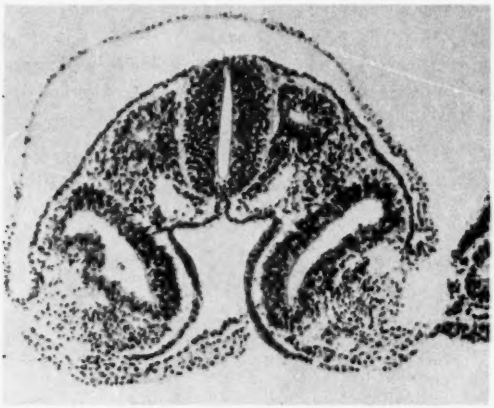

Fig. 2. Photomicrograph of a transverse section of the upper thoracic region of a 16-somite human embryo. The proximity of primitive epidermis and gut to the thin roof and floor plates of the neural tube is well shown. The notochord resembles an outpouching of the primitive gut. The mass of cells streaming anteromedially from each myocele toward the notochord is the sclerotome. (Courtesy Sensing, E. C.: Contributions to Embryology, Institution Pub. No. 583, Vol. 33, Feb. 28, 1949; Carnegie Institution of Washington, Washington, D. C.; Fig. 11, Plate 2.)

This distention subsequently becomes compensated as increasing permeability of the rhombic roof allows fluid to escape and to dissect open the subarachnoid spaces. Should this compensation not occur at the proper time, the continuing imbalance between rate of formation and escape of fluid will cause pathologic overdistention of the tube. Such an obstructive hydrocephalomyelia may become compensated later, or it may persist and, by preventing fluid from adequately dissecting open the absorptive areas in the subarachnoid spaces, may result in communicating hydrocephalomyelia. In this fashion Weed[10] described the embryologic basis for congenital hydrocephalus, which explains why so frequently it is both obstructive and communicating and *so commonly accompanied by hydromyelia.* No more logical explanation has been suggested before or since.

Weed,[10] in his monograph on the normal development, did not mention that embryonal hydrocephalus could cause hindbrain hernia. Chiari, some years before, however, had described in detail various degrees of herniation of the hindbrain

caused by prenatal hydrocephalus. His type-2 herniation subsequently was entitled the *Arnold*-Chiari malformation. Though Chiari's type-1 herniation (pressure coning) now is recognized to be the result of hydrocephalus, by a curious reversal of its discoverer's logic, his type 2 is believed by some to cause it!

Pathologic Anatomy

Previous reports[11,12] have pointed out that the imperforate, distended, neural tube, i.e., obstructive hydrocephalomyelia, which is normal in the embryo, is present also in the infant with myelomeningocele *and* in the adult with syringomyelia; that these pathologic states therefore represent the postnatal persistence of conditions that are physiologic in the embryo; that this obstructive hydrocephalomyelia, uncompensated in myelomeningocele, is compensated in syringomyelia; that each of these states is accompanied by a Chiari or by the Dandy-Walker malformation; and that the infant with myelomeningocele, like the adult with syringomyelia, may have a diverticulum of his hydromyelic central canal constituting a "true syrinx."

In 1876, Leyden[13] came to the conclusion that hydromyelia and syringomyelia are identical, that syringomyelia in the adult is a "rest" of a congenital hydromyelia that "cuts itself off" from the central canal posteriorly. A similar view expressed recently by Greenfield[14] is as follows: "In some cases, especially when hydromyelia is associated with the Arnold-Chiari malformation in the adult, only the ventral wall of the cavity may be covered by ependyma and the remainder by a thick firm layer of neuroglial fibres. Or a syringomyelic cavity may have formed at one side of a hydromyelia. Such cases form a link between hydromyelia and syringomyelia, and are apt to be assigned to one or the other category according to whether or not the cavitation has produced the classical symptoms of syringomyelia during life." From surgical experience with more than 50 cases, I can firmly state that hydromyelia and syringomyelia are one and the same disease.

The adult with syringomyelia therefore has hydromyelia. The adolescent with diastematomyelia has hydromyelia that progresses caudally into the split spinal cord. This is demonstrated in the case of Herren and Edwards[5] and in case 3 of Walker.[15] The infant with myelomeningocele has hydromyelia that progresses caudally into myeloschisis *(Fig. 3),* or into diastematomyelia that in turn progresses into myeloschisis;[3,6] the latter sequence is well illustrated by Benda's[16] case 1. Herren and Edwards[5] point out that there is no normal embryonic stage in which the primitive cord is double, and therefore diastematomyelia must represent the splitting of a single neural tube. The downward anatomic sequence in these infants indicates that hydromyelia is the forerunner of both diastematomyelia and myeloschisis: that increasing distention of the central canal (hydromyelia) progresses to internal rupture of the thin roof and floor plates (diastematomyelia), and then to external rupture through the primitive skin into the amniotic cavity (myeloschisis).

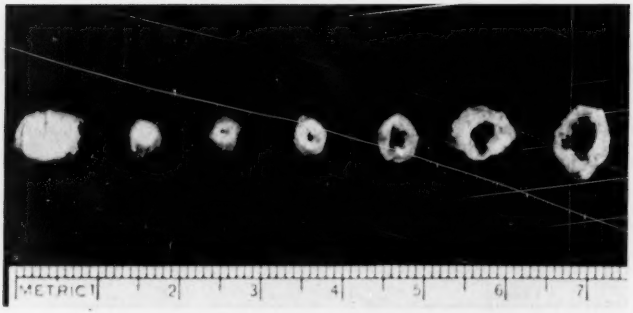

Fig. 3. Photograph of the spinal cord of week-old infant with myelomeningocele and Chiari type-2 malformation. The cervical cord in cross section is bulky and encroaches on the central canal because it has been telescoped from above downward by herniation of the hindbrain. As successive sections approach the myelomeningocele (not shown) the hydromyelia enlarges.

The ontogenetic sequence described above suggests that embryonal hydrocephalomyelia, compensated at the normal time, results in a normal individual; compensated a bit too late it results in symptoms of syringomyelia in adult life; compensated still later, in symptoms of diastematomyelia in adolescence; and uncompensated it results in myelomeningocele in the newborn infant. Thus there is both an ontogenetic as well as an anatomic sequence indicating that myeloschisis represents the rupture of an overdistended neural tube—not a failure to close.

Hypothesis

Any theory that attempts to explain the origin of myelomeningocele, of necessity, must explain the hydrocephalomyelia and the deformity of the hindbrain that accompany it. In a previous paper[11] it was pointed out that, in some instances, myelomeningocele has been accompanied by the Dandy-Walker, or by the Chiari type-1 (pressure coning) instead of the usual Chiari type-2 (Arnold-Chiari) malformation. It was further shown that: each of these malformations of the hindbrain with its accompanying hydrocephalomyelia is the result of embryonal atresia of the fourth ventricle; the large posterior fossa of the Dandy-Walker malformation develops if the coverings of the hindbrain yield more readily to the increased pressure and thus displace the lateral sinuses and attached tentorium in the cephalad direction (i.e., prevent their caudad migration); the small posterior fossa of the Chiari type-2 malformation develops if the coverings of the forebrain expand disproportionately and thus displace the lateral sinuses and tentorium (i.e., cause them to migrate too far) in a caudad direction *(Fig. 4)*.

The sequence of events as they have occurred in the infant born with myelomeningocele and Chiari type-2 malformation I believe to be as follows. *The neural*

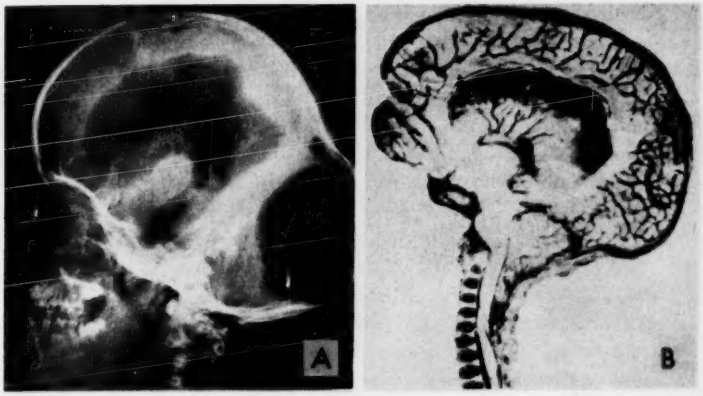

Fig. 4. A, Ventriculogram of an adolescent with Dandy-Walker malformation, illustrating well the disproportionate ballooning of the covering of the hindbrain. (Courtesy of Brodal, A.: Det Norske Vid.-Akad. Skrift. I. Mat.-Naturv. Klasse, No. 3, 1945; Fig. 1, p. 9.) B, Sagittal section of the body of an infant with myelomeningocele and Chiari type-2 malformation. The coverings of the hindbrain appear to have been compressed by the disproportionate ballooning of the coverings of the forebrain. (Courtesy of Moncrieff, A., and Norman, R. M.: Greenfield, J. G.: *Neuropathology;* Edward Arnold (Publishers) Ltd., 1958, p. 314.)

tube, shortly after closure, becomes overdistended because of inadequate permeability of the rhombic roof. The latter, perhaps, may result from maternal illness, avitaminosis, radiation, ingestion of substances toxic to embryonal tissue, or genetic influences. *The lining neuroepithelium responds to stretching, by more active cell reproduction. The increased intraluminal pressure, transmitted equally in all directions, causes the tube to expand disproportionately in areas where its coverings happen to be more yielding.* These areas are usually at the cephalad and the caudal ends where somites are less mature. *The forebrain balloons and displaces the hindbrain and its coverings caudally,* thus reducing the size of the posterior cranial fossa. In 26 cases of Chiari type-2 malformation, Daniel and Strich[17] found the posterior fossa invariably small, the tentorium cerebelli being attached close to the large foramen magnum. *As the intraluminal pressure continues to rise, a localized or splitting (diastematomyelia), bulging (syringomyelocele), followed by rupture (myeloschisis) will occur at the more immature caudal segments.* Myeloschisis therefore is rupture of the lumen of the neural tube caused by obstructive hydrocephalus. It occurs before the spinal subarachnoid space has developed.* The level of the rupture is determined by the embryonic age, i.e., the number of somites existing at the time of rupture. *The ensuing*

* *Meningocele arises after the spinal subarachnoid space has developed but before chondrification of the neural arches has taken place. It represents a posterior bulging of the subarachnoid space caused by communicating hydrocephalus. It does not rupture because the later occurring communicating hydrocephalus is less severe, is more readily compensated, and the investing skin is tougher.*

* Splitting AND bulging should be REVERSED in the sentence. See ERRATA P. 184, V. 27, No. 3, 1960

collapse of the head causes its redundant lining of neural tissue to wrinkle. This explains the plication and overgrowth found by Patten[18] in his human embryo with myeloschisis. Relief of hydrocephalus by rupture of the tube explains why Warkany, Wilson, and Geiger[19] found that in their rats with experimental myeloschisis, hydrocephalus was absent and, conversely, that in litter mates without myeloschisis it was present. *The discharge of ventricular fluid into the amniotic sac removes the hydrostatic pressure essential to the normal dissection of the subarachnoid spaces.*[10]

With the maturation of the embryo, the small posterior fossa cannot contain the growing hindbrain, which therefore squeezes downward through the foramen magnum (and also upward through the incisura[6]*).* This mechanism, likewise, is corroborated by the findings of Warkany, Wilson, and Geiger[19] that in fetal rats up to 17 days with myeloschisis, hindbrain hernia was absent, while in all those more than 21 days it was present. *When the downward herniation has reached a stage that causes buckling of the medulla on the telescoped cervical cord (Chiari type-2 malformation), the kinked central canal (Fig. 5) is closed off and obstructive hydrocephalus is re-established.* The ventricular fluid then escapes through the attenuated (perhaps ruptured) ventricular wall, but too late for it to dissect open the absorbing areas in the subarachnoid space. *The pressure of subarachnoid fluid anterior to the cord turns the open portion of the cord inside out to form the sac of a myelomeningocele.* This explains the absence of cord tissue in the spinal canal at the level of the sac. *If*

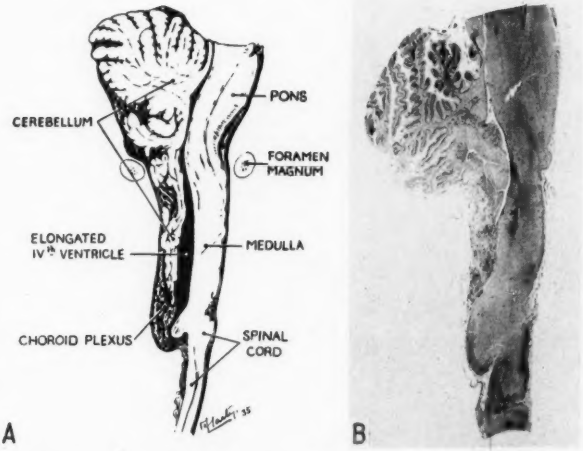

Fig. 5. These illustrations suggest that obliteration of the involved portion of the central canal in the Chiari type-2 malformation is the result of kinking and telescoping. (A, Courtesy of Russell, D. S.: M. Res. Council Special Rep. Ser. No. 265; H. M. Stationery Office, 1949; The Controller, H. M. Stationery Office, 1959; Fig. 11, p. 23. B, Courtesy of Cameron, A. H.: J. Path. & Bact. 73: 195-211, 1957; Fig. 2, plate LIV.)

* Should be CRANIOSCHISIS
See ERRATA P. 184, V. 27, No. 3, 1960

rupture of the attenuated sac occurs, subarachnoid fluid escapes and hydrocephalus once more may be relieved. This second rupture explains some cases of myelomeningocele with Chiari type-2 malformation but without hydrocephalus.[6,20]

The blood vessels nourishing the exposed neural tissue, distend because of lack of overlying tissue support. Thus originates the area medullovasculosa described by Von Recklinghausen.[1]

Other Associated Anomalies

Morgagni's[7] hydromyelic theory will explain every anomaly associated with myelomeningocele. The mechanism of formation of the Chiari type-1, Chiari type-2, and Dandy-Walker malformations have been described. Secondary distortion of surrounding tissues caused by the overdistention of the neural tube renders unnecessary the premise[21] that there must be associated *primary* disturbances in ectoderm, mesoderm, or endoderm to explain the accompanying dysplasias of skin, skeleton, muscle, genitourinary or gastrointestinal tracts.

In severe Chiari type-2 hindbrain herniation the midbrain is displaced caudally into the small posterior fossa *(Fig. 6).* Here its previously overdistended lumen is compressed by growth of the brain in this confined space just as is the fourth ventricle. This explains the associated stenosis and forking (plication) of the aqueduct, and confirms MacFarlane and Maloney's[22] suggestion that it is due to "a generalized compression of the hind end of the ventricular system." A beak-like deformity of the tectal plate[23] shown in *Figure 4B* is an integral part of the midbrain compression.

Enlargement of the massa intermedia[6] results from the enlarging sagittal diameter of the head, which by increasing the tension of the mesial walls of the forebrain causes closer approximation of the thalami.[12] Attenuation of the falx, interdigitation of the mesial convolutions of the cerebral hemispheres,[6] enlargement of the foramens of Monro, and fenestration of the septum pellucidum also are, at least in part, due to this stretching in the sagittal plane. Microgyria develops from plication of redundant neural tissue occurring at the time of rupture. Heterotopic nodules of cortex in the walls of the ventricles are the result of deep infolding of cortical tissue in these plications, and therefore are of the same significance as microgyria. This is corroborated by the studies of Cameron[6] who found that, in the presence of such heterotopic nodules, the overlying, highly convoluted cortex dips deeply down into the white matter to reach within a fraction of a millimeter of the nodules.

The glial nests in the meninges[24] represent extrusions through the primitive pia produced by increased intraluminal pressure. There is similar glial heterotopia in the adult with syringomyelia,[24] and the neoplasia [3,5,25] accompanying each of these states probably arises from these displaced embryonal cell rests.

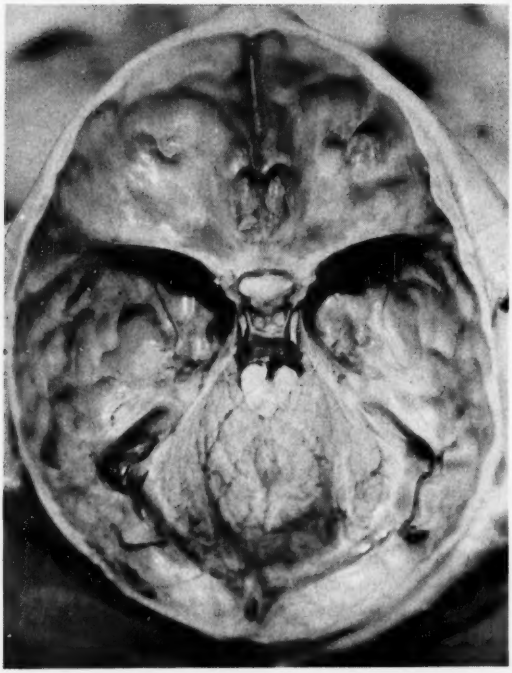

Fig. 6. Necropsy photograph. Child aged four years and five months had Chiari type-2 malformation, congenital hydrocephalus, and myelomeningocele. The hydrocephalic forebrain has been removed. The entire attachment of the tentorium is dislocated caudally including the superior petrosal sinuses which are depressed well below the petrous ridges. Note that the cerebral peduncles are displaced downward behind the clivus into the posterior fossa while the superior surface of the vermis bulges upward through the incisura. The aqueduct, compressed in the midbrain hernia, cannot be visualized. This necropsy study illustrates the advantages of fixation in situ and removal of the hydrocephalic cerebral hemispheres before disturbing the relationship of the structures of the posterior fossa. (Gardner, W. J.: Cleveland Clin. Quart. 26: 206-222; Oct. 1959, Fig. 4, p. 210.)

Diastematomyelia results when the increased intraluminal pressure causes separation of the roof plate, permitting the lateral plates to open like a book that is subsequently torn along its binding; i.e., the floor plate. (The layer of tissue reinforcing the roof plate is thinner than that of the floor plate; therefore, the roof plate separates more readily. This mechanism also will explain the pronounced tendency for syringomyelic cavities to involve the posterior columns.) Each lateral plate thus *rotated through 90 degrees* will form an imperfect hydromyelic cord above the level at which external rupture has resulted in myeloschisis.

The finding at necropsy of myelodysplasia without hydromyelia does not prove that it was not the result of pre-existing hydromyelia. Since the physiologic

degree of hydromyelia present in every normal embryo becomes compensated, there is no reason that a pathologic degree likewise should not become compensated at least in mild cases. Such compensation occurring early enough will permit the growing spinal cord to encroach on its distended lumen.

Likewise, the occasional finding of ventricles of normal size in cases of microgyria or Chiari malformation does not prove that there was not pre-existing hydrocephalus subsequently reduced by compensation or by rupture of the neural tube. Similarly, the overgrowth and excessive plication of the neural tubes of Patten's[18] embryos that did *not* have myeloschisis, could have resulted from hydrocephalomyelia either compensated during the life of the embryo, or reduced after death by cerebrospinal fluid absorption occasioned by its low colloid osmotic tension.

In some instances of myelodysplasia, as in those reported by Walker,[15] a dilated vertebral canal may constitute the only evidence of a pre-existing dilatation of the neural tube. Holtzer[26] has shown experimentally that the diameter of the developing spinal canal is determined by the diameter of the neural tube that it encloses. He states that: "Migrating pre-cartilage cells respond in a discriminatory and stereotyped fashion to the presence of any neural tissue. By maintaining a characteristic distance from the neural tissue the pre-cartilage cells are deployed in such a fashion that a lumen will eventually be formed in the cartilage whose size is a function of the enclosed nerve bundle." This work of Holtzer also explains the mid-line bony spur separating the cords in diastematomyelia.

Craniolacunia represents interference with chondrification, and subsequent ossification caused by compression and stretching of the mesodermal anlage of the skull. Separation and distortion of the paired sclerotomes by the overdistended neural tube will explain spina bifida posterior, spina bifida anterior (hemivertebrae), dilated vertebral canal, scoliosis, fused vertebrae, and deformities of ribs and sternum; distortion of the neighboring limb buds—the club feet; distortion of the overlying ectoderm—cutaneous dysplasia; distortion of the intermediate mesoderm—deformities of the genitourinary tract; distortion and adhesion to the wall of the primitive gut—alimentary diverticuli and cysts described by Saunders,[27] and by McLetchie, Purves, and Saunders.[28]

Finally, a simultaneous rupture of the roof plate into the amniotic sac, and of the floor plate into the primitive gut will explain the rare, usually stillborn infants in whom a fistula of the gut opens onto the floor of a myeloschisis *(Fig. 7)*. This makes it unnecessary to invoke Bremer's[29] purely hypothetic "accessory neurenteric canal" or any of the other earlier theories that Saunders[27] has summarized in his review and to which the reader is referred.

Conclusions

Therefore we find that Morgagni's hydromyelic theory is less fragile than Von Recklinghausen's araphic theory; that Morgagni's theory will explain the vertical

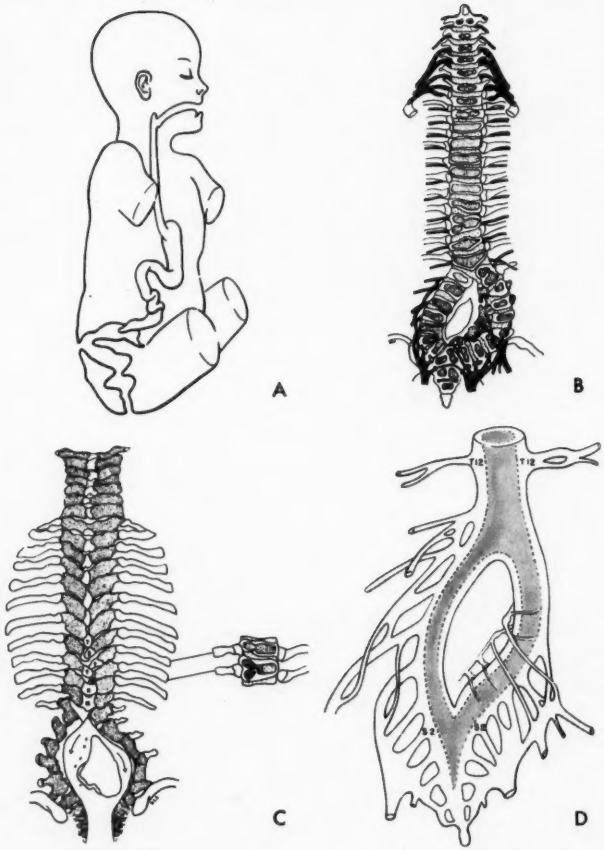

Fig. 7. These illustrations are redrawn from Saunders'[27] case of a child who survived five months with a fistula of the colon opening onto the back through a completely bifid vertebral column and cord. This represents spontaneous healing of a myeloschisis that had ruptured anteriorly into the primitive gut as well as posteriorly through the skin. Diagram: A, Mucosa of colon had grown to the skin. B, Spine viewed from the front. C, Spine viewed from the back. D, The divided cord was hydromyelic; two sets of nerves arose from the left division.

anatomic sequence from mild hydromyelia to myeloschisis, the transverse anatomic sequence from occult spina bifida to combined anterior and posterior myeloschisis, the ontogenetic sequence from syringomyelia in the adult to myelomeningocele in the infant, and also the many anomalies associated with myelomeningocele which are present in the brain and other structures.

Acknowledgment

The author, as a clinician, wishes to acknowledge his indebtedness to those in other fields, particularly to the fundamental contribution of Weed on the embryonal development of the cerebrospinal fluid spaces, to Chiari, to Russell, to Saunders, and to Cameron for their contributions on the pathology, and to Holtzer, to Fowler, and to Warkany, Wilson, and Geiger for their experimental contributions.

References

1. von Recklinghausen, F.: Untersuchungen über die Spina bifida. Arch. path. Anat. **105:** 243; 373, 1886.
2. Cameron, A. H.: Spinal cord lesion in spina bifida cystica. Lancet **2:** 171-174, 1956.
3. Weil, A., and Matthews, W. B.: Duplication of spinal cord, with spina bifida and syringomyelia. Arch. Path. **20:** 882-890, 1935.
4. Kapsenberg, J. G., and van Lookeren Campagne, J. A.: Case of spina bifida combined with diastomatomyely, anomaly of Chiari and hydrocephaly. Acta nat. **7:** 366-388, 1949.
5. Herren, R. Y., and Edwards, J. E.: Diplomyelia (duplication of spinal cord). Arch. Path. **30:** 1203-1214, 1940.
6. Cameron, A. H.: Arnold-Chiari and other neuro-anatomical malformations associated with spina bifida. J. Path. & Bact. **73:** 195-211, 1957.
7. Morgagni, G. B.: De Sedibus et Causis Morborum 1761. Trans. by B. Alexander. London: A. Millar and T. Cadell, 1769.
8. Patten, B. M.: Embryological stages in establishing of myeloschisis with spina bifida. Am. J. Anat. **93:** 365-395, 1953.
9. Fowler, I.: Responses of chick neural tube in mechanically produced spina bifida. J. Exper. Zoöl. **123:** 115-151, 1953.
10. Weed, L. H.: The Development of the Cerebro-Spinal Spaces in Pig and in Man. Washington, D. C.: Carnegie Inst., 1917, 116 pp., 4°.
11. Gardner, W. J.: Anatomic features common to Arnold-Chiari and Dandy-Walker malformations suggest common origin. Cleveland Clin. Quart. **26:** 206-222, 1959.
12. Gardner, W. J.: Anatomic anomalies common to myelomeningocele of infancy and syringomyelia of adulthood suggest common origin. Cleveland Clin. Quart. **26:** 118-133, 1959.
13. Leyden, E.: Ueber Hydromyelus und Syringomyelie. (About hydromyelia and syringomyelia.) Arch. path. Anat. **68:** 1-26, 1876.
14. Greenfield, J. G., and others: Neuropathology. London: Edward Arnold (Publishers) Ltd., 1958, 640 pp.
15. Walker, A. E.: Dilatation of vertebral canal associated with congenital anomalies of spinal cord. Am. J. Roentgenol. **52:** 571-582, 1944.
16. Benda, C. E.: Dysraphic states. J. Neuropath. & Exper. Neurol. **18:** 56-74, 1959.

17. Daniel, P. M., and Strich, S. J.: Some observations on congenital deformity of central nervous system known as Arnold-Chiari malformation. J. Neuropath. & Exper. Neurol. **17:** 255-266, 1958.

18. Patten, B. M.: Overgrowth of neural tube in young human embryos. Anat. Rec. **113:** 381-393, 1952.

19. Warkany, J.; Wilson, J. G., and Geiger, J. F.: Myeloschisis and myelomeningocele produced experimentally in rat. J. Comp. Neurol. **109:** 35-64, 1958.

20. Russell, D. S., and Donald, C.: Mechanism of internal hydrocephalus in spina bifida. Brain **58:** 203-215, 1935.

21. Lichtenstein, B.: "Spinal dysraphism"; spina bifida and myelodysplasia. Arch. Neurol. & Psychiat. **44:** 792-810, 1940.

22. MacFarlane, A., and Maloney, A. F. J.: Appearance of aqueduct and its relationship to hydrocephalus in Arnold-Chiari malformation. Brain **80:** 479-491, 1957.

23. Feigin, I.: Arnold-Chiari malformation with associated analogous malformation of midbrain. Neurology **6:** 22-31, 1956.

24. Cooper, I. S., and Kernohan, J. W.: Heterotopic glial nests in subarachnoid space: histopathologic characteristics, mode of origin and relation to meningeal gliomas. J. Neuropath. & Exper. Neurol. **10:** 16-29, 1951.

25. Poser, C. M.: The Relationship Between Syringomyelia and Neoplasm. Pub. No. 262, Am. Lect. Ser., monograph in Am. Lect. in Neurol., edited by C. D. Aring. Springfield, Ill.: Charles C Thomas, Pub., 1956, 98 pp.

26. Holtzer, H.: Experimental analysis of development of spinal column. Part I. Response to precartilage cells to size variations of spinal cord. J. Exper. Zoöl. **121:** 121-147, 1952.

27. Saunders, R. L. deC. H.: Combined anterior and posterior spina bifida in living neonatal human female. Anat. Rec. **87:** 255-278, 1943.

28. McLetchie, N. G. B.; Purves, J. K., and Saunders, R. L. deC. H.: Genesis of gastric and certain intestinal diverticula and enterogenous cysts. Surg. Gynec. & Obst. **99:** 135-141, 1954.

29. Bremer, J. L.: Dorsal intestinal fistula; accessory neurenteric canal; diastematomyelia. A. M. A. Arch. Path. **54:** 132-138, 1952.

THALASSEMIA INTERMEDIA—BIOCHEMICAL AND GENETIC CONSIDERATIONS

Report of a Case

FERNANDO L. GARZÓN, M.D.,* JOHN D. BATTLE, JR., M.D.,
Department of Hematology

and

LENA A. LEWIS, Ph.D.
Division of Research

THALASSEMIA intermedia is a syndrome with clinical and hematologic manifestations ranging in severity between those observed in thalassemia minor and in thalassemia major (Cooley's anemia).[1-6] The qualifying term intermedia emphasizes the lack of basic knowledge concerning the biochemical and the genetic abnormalities of the various thalassemia syndromes. This paper reports the occurrence of homozygous thalassemia intermedia in an adult with approximately 80 per cent fetal hemoglobin and 3.5 per cent A_2 hemoglobin. The parents and the two children of the patient have thalassemia minor with fetal hemoglobin values in a range of 10 to 17 per cent.

Report of a Case

The propositus, a 37-year-old white man of Croatian descent was first examined at the Cleveland Clinic in September, 1955, because of recurrent superficial suppurative lesions of the legs. In 1940 he underwent an appendectomy; at that time he was told that the spleen was enlarged. In 1947, a mild anemia and enlargement of the spleen were diagnosed as Mediterranean anemia. Jaundice was reported to have been present on several occasions. There were no other specific symptoms. He stated that he never had ulcers of the lower extremities. He had had no symptoms suggestive of biliary colic, and had lost no time from his work as a draftsman.

Physical examination revealed a tall thin man. The mucosae were slightly pale and the sclerae were jaundiced. There were numerous pigmented scars on the anterior aspect of the legs, and an ecthymiform lesion on the right calf. No ulcers were present. Superficial varicose veins and evidence of chronic stasis were present on the lower extremities. The spleen was firm and descended 12 cm. below the costal margin. The edge of the liver was palpable 6 cm. below the costal margin. The results of the examination of the heart, chest, and lungs were normal. The blood pressure was 130/68 mm. of Hg. A roentgen examination showed that the chest, skull, and hands were normal. The cholecystographic study revealed evidence of multiple nonopaque stones.

The patient has been under periodic observation since 1955, and the extent of the hepatosplenomegaly and the severity of jaundice have not changed. The mild hemolytic disease remains well compensated.

*Fellow in the Department of Hematology.

Results of the physical examinations of the parents and the two children of the patient were normal. None of them had splenomegaly, pallor, or jaundice.

Hematologic data. The erythrocyte count of the patient ranged between 4,200,000 and 5,200,000 per cubic millimeter with anisochromia, anisocytosis, and poikilocytosis with oval, tailed, teardrop, and target cells. The hemoglobin has ranged from 10.2 gm. to 12.5 gm. per 100 ml. The reticulocyte count has ranged from 1 to 3.4 per cent. The leukocyte and differential counts have always been within normal limits. The mechanical fragility of the patient's erythrocytes was 4 per cent (normal is 6 per cent). The quantitative osmotic fragility began at a concentration of 0.36 per cent of sodium chloride and was not complete at 0.10 per cent. The test for sickling was negative. The radiochromate-erythrocyte survival study revealed an apparent half-life of 24 days. The range of normal values in our laboratory is from 28 to 32 days. The serum bilirubin was 0.28 mg. per 100 ml., direct, and 3.0 mg. per 100 ml., indirect. The patient's fetal hemoglobin, determined by the alkali denaturation method of Singer, Chernoff, and Singer[7] ranged between 78 and 83 per cent. The remainder of the hematologic data of the patient and his family is summarized in *Table 1.*

Electrophoretic Studies of Hemoglobin

Studies of the hemoglobin solutions were made by electrophoresis on paper, using barbiturate buffer, pH 8.6, μ 0.05; on agar using citric acid-citrate buffer,[8] pH 6.2, 0.05 molarity; on starch gel using borate-tris buffer,[9] pH 8.2; and on starch block using barbiturate buffer,[10] pH 8.6, μ 0.05. A sample of the patient's hemoglobin was chromatographed using amberlite IRC 50 (XE 64)[11] and citrate buffer, pH 6.0, sodium-ion concentration 0.15, for elution.

Table 1.—*Hematologic data of patient and family*

Family relation; age, years	Erythrocytes, million/cu. mm.	Hemoglobin, gm./100 ml.	Mean corpuscular volume, cu. μ	Reticulocytes, percentage of total
Patient 37	4.2-5.2	10.2-12.5	80-82	1-3.4
Father 60	5.3	12.2	80	3.2
Mother 56	4.8	10.8	80	4.5
Daughter 10	5.0	12.0	78	1.6
Son 9	4.3	9.5	78	2.2
Wife	4.7	12.4	87	Not determined

Results obtained by paper electrophoresis indicated that approximately 90 per cent of the patient's hemoglobin had a mobility similar to that of fetal hemoglobin. To establish its identity more conclusively the material was subjected to chromatographic analysis. The characteristics of the major fraction of the patient's hemoglobin corresponded perfectly with those of samples of known fetal hemoglobin. The hemoglobins of the patient and his family, when studied by electrophoresis on agar, showed a fraction with mobility faster than that of normal adult hemoglobin (A_1) and identical with that of known fetal hemoglobin *(Fig. 1)*. Both parents and both children of the patient had high concentrations of fetal hemoglobin *(Table 2)*.

Discussion

Though much information has been acquired in the past thirty years in regard to thalassemia, there are still many puzzling biochemical and genetic aspects. On the basis of the familial distribution of thalassemia it has been suggested[1,12-14] that the mild form of the disease, known as thalassemia minor, occurs when there is heterozygosity for a gene that in the homozygous state produces the more severe thalassemia major. The genetics of thalassemia would follow the pattern depicted by Valentine and Neel[14] *(Fig. 2)*. However, the mechanism is much more complex. On the basis of Valentine and Neel's simple hypothesis, it is difficult to explain the great variation in the clinical, hematologic, and biochemical manifestations of thalassemia. The spectrum of the thalassemia syndromes ranges from those characterized by minimal erythrocytic abnormalities to tha-

Table 1.—*Continued*

Erythrocyte abnormalities	Fetal hemoglobin,* percentage of total	Diagnosis
Anisochromia, anisocytosis, poikilocytosis; oval, tailed, teardrop, and target cells	78-83	Thalassemia intermedia
Anisocytosis, poikilocytosis; oval, tailed, and target cells	10	Thalassemia minor
Anisochromia, anisocytosis, poikilocytosis; oval, tailed, and target cells	14	Thalassemia minor
Anisocytosis, poikilocytosis; oval and target cells	17	Thalassemia minor
Anisochromia, anisocytosis, poikilocytosis; oval and target cells	13	Thalassemia minor
None	1.2	Normal

*Measured according to the alkali denaturation method of Singer, Chernoff, and Singer.[7]

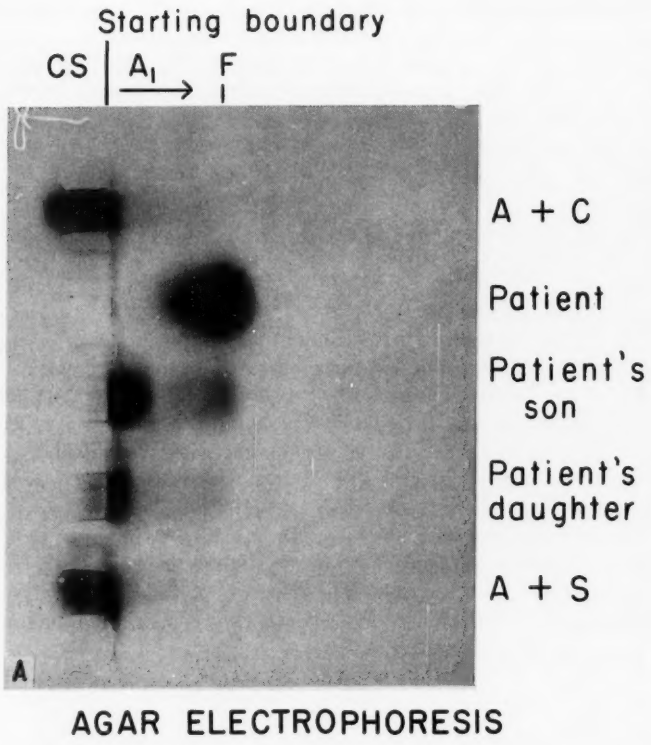

Fig. 1 A. Electrophoretic patterns of hemoglobin of the patient and his family; agar electrophoresis.

lassemia major characterized by a severe hemolytic anemia, splenomegaly, bone changes, and a greatly shortened life span of the patient. Thalassemia intermedia, between these two extremes, may present a complicated genetic pattern that is heterozygous, doubly heterozygous, or homozygous *(Fig. 3)*. Double heterozygosity represents a combination of genes for thalassemia and for abnormal hemoglobins, for example, sickle-thalassemia. The complexity of the problem is further illustrated by the occasional lack of correlation between the clinical severity of the disease and the hemoglobin abnormalities. In thalassemia, the percentage of fetal hemoglobin usually is higher in the homozygous states. Our patient, in spite of having approximately 80 per cent of fetal hemoglobin, had only a mild hemolytic anemia. Other observations have been recorded[15] in which adult members of a number of families, each with a great percentage of fetal hemoglobin, have had only mild erythrocytic abnormalities.

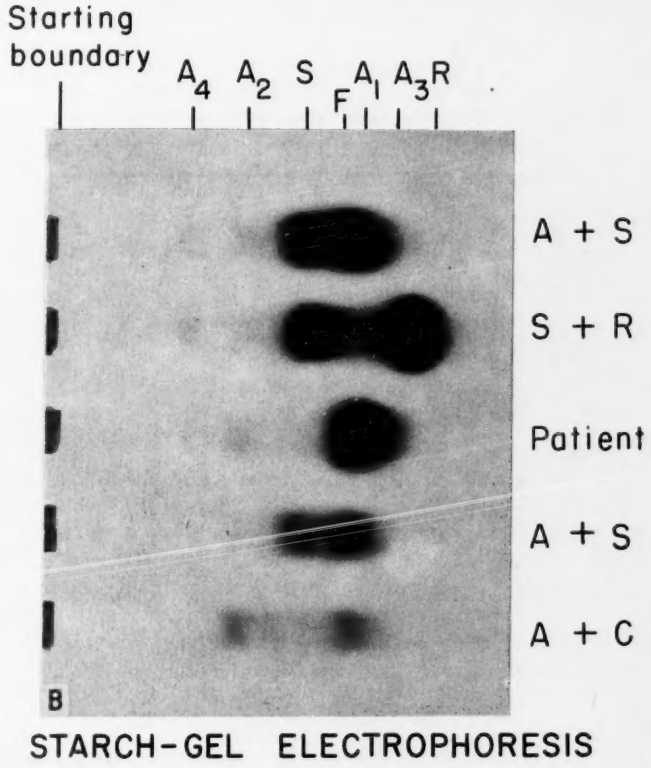

Fig. 1 B. Electrophoretic patterns of hemoglobin of the patient and his family; starch-gel electrophoresis.

In 1955, Kunkel and Wallenius[10] applied the technic of starch-block electrophoresis (pH 8.6) to the separation of hemoglobin. They found that normal adult hemoglobin separated into three components: main (A_1), slow (A_2), and fast (A_3). Masri, Josephson, and Singer[16] reported the presence of another component, A_4, with mobility slower than A_2. The maximal normal concentration of A_2 is 3.5 per cent. It is usually high in thalassemia, yet Kunkel and Wallenius[10] reported several patients with homozygous thalassemia and normal amounts of A_2. The affected members of our patient's family had increased amounts of A_2 hemoglobin with the exception of the son of the propositus. The values of A_2 show no correlation with the clinical severity of thalassemia, nor is there any apparent correlation of the amount of A_2 with that of fetal hemoglobin.[17]

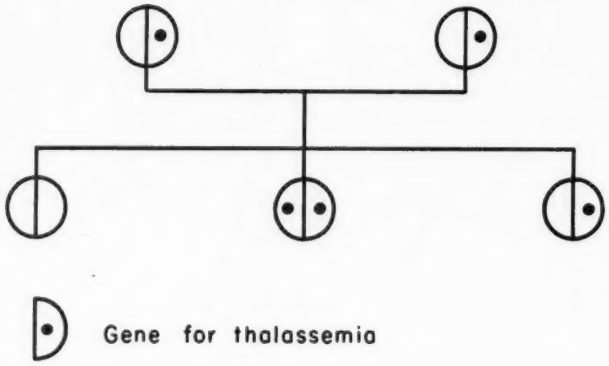

Fig. 2. Genetic mechanism of thalassemia (after Valentine and Neel[14]).

Table 2.—*Electrophoretic studies of hemoglobin of patient and family*

Family relation	Type of hemoglobin, percentage of total					Supporting medium used
	F	A_1	A_2	A_3	A_4	
Patient	89.6*	—	3.5	3.8	2.1	Starch gel and starch block
	90	10	—	—	—	Agar
Father	89.6*	—	3.5	4.8	2.1	Starch gel
	15	85	—	—	—	Agar
Mother	87.9*	—	4.6	5.5	2.0	Starch gel
	15	85	—	—	—	Agar
Daughter	85*	—	4.5	4.5	6.0	Starch gel and starch block
	10	90	—	—	—	Agar
Son	92.2*	—	2.3	4.0	1.5	Starch gel and starch block
	15	85	—	—	—	Agar

*Resolution of F and A_1 not clear; therefore percentages include both.

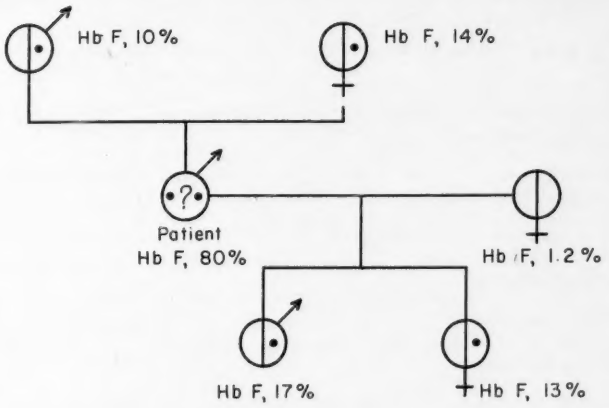

Fig. 3. Pedigree of the family of the patient reported, with individual percentages of fetal hemoglobin.

The preceding considerations seem to lend support to the concepts of Chernoff[15,18,19] in regard to the genetics of thalassemia. He suggests that the thalassemia syndromes are caused by a series of multiple, interrelated genetic defects, not necessarily closely linked, which in various combinations give rise to a graduated series of hematologic aberrations from a mild asymptomatic state to thalassemia major. He speculates that at least one of the genes involved in the thalassemia syndromes is either identical with or closely related to the gene for fetal hemoglobin. Some patients may well be homozygous for the hemoglobin-F gene, and heterozygous for genes that control other manifestations of thalassemia. This might be the genetic explanation of the high percentage of fetal hemoglobin in our patient in spite of his position in the intermediate area of the thalassemia spectrum.

Summary

A case report is presented of a patient having thalassemia intermedia with a high percentage of fetal hemoglobin (78 to 83 per cent) and a mild, compensated hemolytic anemia. It is suggested that the patient may be homozygous for the hemoglobin-F gene, but perhaps heterozygous for genes responsible for other manifestations of thalassemia.

References

1. Dameshek, W.: Familial Mediterranean target-oval cell syndromes. Am. J. M. Sc. **205**: 643-660, 1943.

2. Smith, C. H.: Detection of mild types of Mediterranean (Cooley's) anemia. Am. J. Dis. Child. **75**: 505-527, 1948.

3. Chini, V., and Malaguzzi Valeri, C.: Mediterranean hemopathic syndromes. Blood **4:** 989-1013, 1949.

4. Astaldi, G., and Tolentino, P.: Physiopathologie et clinique de la thalassémie. Sang **23:** 453-468, 1952.

5. Gatto, I.: Thalassemia (microkarterocytosis) and drepanocytosis; their forms and genetics. Acta genet. med. et gemel. **2:** 19-29, 1953.

6. Sturgeon, P.; Itano, H. A., and Bergren, W. R.: Genetic and biochemical studies of 'intermediate' types of Cooley's anaemia. Brit. J. Haemat. **1:** 264-277, 1955.

7. Singer, K.; Chernoff, A. I., and Singer, L.: Studies on abnormal hemoglobins; their demonstration in sickle cell anemia and other hematologic disorders by means of alkali denaturation. Blood **6:** 413-428, 1951.

8. Robinson, A. R.: Discussion. Part III. Abnormal Hemoglobins. *In* Conference on Hemoglobin. Washington, D. C.: National Academy of Sciences-National Research Council. Pub. **557:** 1958, 303 pp., pp. 176-178.

9. Owen, J. A., and Got, C.: Electrophoresis of human haemoglobins in starch gel. Clin. chim. acta **2:** 588-589, 1957.

10. Kunkel, H. G., and Wallenius, G.: New hemoglobin in normal adult blood. Science **122:** 288, 1955.

11. Huisman, T. H. J., and Prins, H. K.: Chromatographic estimation of four different human hemoglobins. J. Lab. & Clin. Med. **46:** 255-262, 1955.

12. Caminopetros, J.: Recherches sur l'anémie érythroblastique infantile, des peuples de la Méditerranée orientale; étude nosologique. Ann. méd. **43:** 27-61, 1938.

13. Caminopetros, J.: Recherches sur l'anémie érythroblastique infantile, des peuples da la Méditerranée orientale; étude antropologique, étiologique et pathogénique; la transmission héréditaire de la maladie. Ann. méd. **43:** 104-125, 1938.

14. Valentine, W. N., and Neel, J. V.: Hematologic and genetic study of transmission of thalassemia (Cooley's anemia; Mediterranean anemia). Arch. Int. Med. **74:** 185-196, 1944.

15. Chernoff, A. I.: Medical progress; human hemoglobins in health and disease. New England J. Med. **253:** 322-331; 365-374; 416-423, 1955.

16. Masri, M. S.; Josephson, A. M., and Singer, K.: Starch block electrophoretic studies of human hemoglobin solutions. I. Technic and results in normal adult. Blood **13:** 533-542, 1958.

17. Josephson, A. M.; Masri, M. S.; Singer, L.; Dworkin, D., and Singer, K.: Starch block electrophoretic studies of human hemoglobin solutions. II. Results in cord blood, thalassemia and other hematologic disorders; comparison with Tiselius electrophoresis. Blood **13:** 543-551, 1958.

18. Chernoff, A. I.: Human hemoglobins: current status. Am. Pract. Digest. Treat. **9:** 569-581, 1958.

19. Chernoff, A. I.: The Thalassemia Syndromes. Part V. Clinical Characteristics Associated with Abnormal Hemoglobins. *In* Conference on Hemoglobin. Washington, D. C.: National Academy of Sciences-National Research Council Pub. **557,** 1958, 303 pp., pp. 283-286.

BENIGN LYMPHOEPITHELIAL CYSTS (ECTOPIC SALIVARY GLAND TISSUE) IN LYMPH NODES

Report of Two Cases

ELDON R. DYKES, M.D.,* ROBIN ANDERSON, M.D.,
Department of Plastic Surgery
and
WILLIAM A. HAWK, M.D.
Department of Anatomic Pathology

CYSTIC changes in a cervical lymph node containing ectopic salivary gland tissue are rarely seen by the pathologist and are highly confusing to the surgeon; this is the report of two such cases.

Case Reports

Case 1. A 42-year-old woman, a school teacher, had been treated at the Cleveland Clinic for several years for an anxiety tension state and mucous colitis. On July 22, 1958, during a routine physical examination a 0.5-cm. firm, solitary nodule was palpated in the right lobe of the thyroid gland. In the right digastric triangle adjacent to the right submaxillary salivary gland a 2.0-cm. firm mass believed to be a lymph node was felt. The results of the remainder of the physical examination and of the laboratory and roentgen studies were within normal limits.

On July 30, 1958, a lobectomy of the right side of the thyroid was performed. There was no lymphadenopathy in the vicinity of the thyroid gland. The nodule in the thyroid was diagnosed as papillary carcinoma. In view of this diagnosis, it was considered advisable to start desiccated thyroid therapy immediately. During this treatment, from August through January, the submaxillary node remained unchanged. On January 26, 1959, the node was excised. The patient has continued the thyroid therapy for the papillary carcinoma and has done well to the date of this writing.

The gross excised specimen was soft, ovoid, and reddish-tan, measuring 1.1 cm. in its greatest dimension. A thin fibrous capsule was noted. The cut surface was moist, tan, and stippled with yellow puncta that were less than 0.1 cm. in diameter.

The microscopic findings confirmed the encapsulated nature of the lesion. A peripheral sinus and lymphoid follicles characteristic of a lymph node were found in the peripheral or cortical areas. The hilus of the node was also included in sections and contained afferent and efferent lymphatics. A small amount of salivary gland tissue was present immediately adjacent to the node at the hilus. Scattered throughout the lesion were numerous cystic structures of various sizes *(Fig. 1)*. The largest ones measured up to 1.5 mm. in diameter, and the smaller cysts were approximately 100 to 200 μ in diameter. Most of the smaller cysts were arrayed in small clusters. Each cyst was lined with squamous epithelial cells, this pavement epithelium ranging from 1 cell to 6 cells in thickness *(Figs. 2 and 3)*. In some cysts a delicate fibrous enveloping layer was present, and the epithelial cells appeared to rest upon this. However, in many

**Fellow in the Department of Plastic Surgery.*

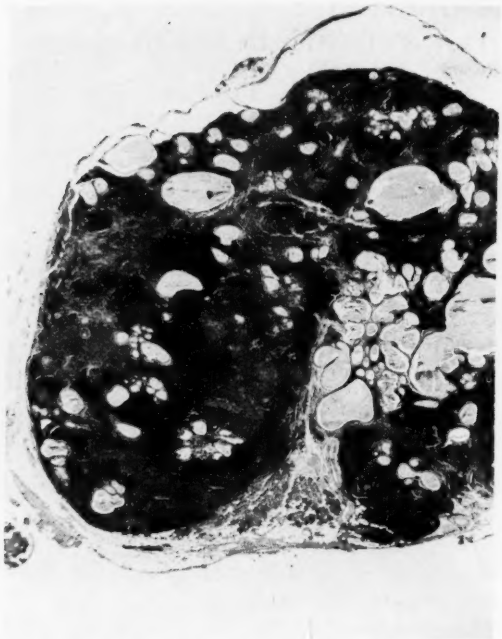

Fig. 1. Photomicrograph of a section of a cervical lymph node, showing numerous large and small cysts scattered throughout. Lymph follicles and a portion of peripheral sinus are at the left. A small island of salivary gland tissue is outside the node at the hilus. Hematoxylin-eosin—methylene blue stain; magnification X 12.

cysts this fibrous layer was discontinuous. Many of the cysts contained amorphous acidophilic material, and in a few there was infiltration by histiocytes and neutrophils. No transmural migration of lymphocytes was noted. Occasional small solid islands of epithelial cells were also present.

Case 2. A 59-year-old man was examined for a mass, posterior to the left ear, which had been present one year. During the past three months the patient had noted discomfort upon turning his head to the left. There were no other symptoms related to the mass. An irregular, movable, nontender, 3.5-cm. mass was palpated adjacent to the posterior border of the left parotid gland. This mass appeared to extend into the space behind the mandible and posteriorly beneath the sternocleidomastoid muscle. On March 25, 1960, this area was explored surgically. Several lymph nodes were removed from the area adjacent to the posterior border of the parotid gland. No other masses were present.

The largest node measured 2.0 cm. in diameter; the smallest was 0.3 cm. in diameter. The gross and microscopic pathologic findings were identical to those described for the specimen in case 1.

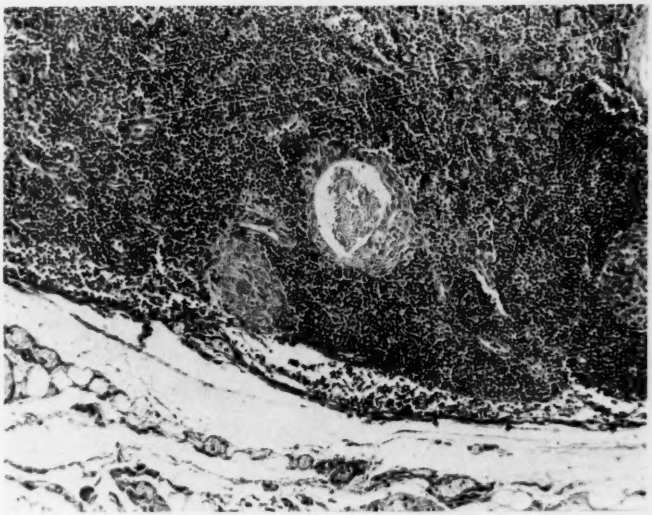

Fig. 2. Photomicrograph of a section of a cervical lymph node, showing a small cyst and squamous epithelial island just above the peripheral sinus of the node. Masson trichrome stain; magnification X 120.

Discussion

Three groups of lymph nodes are associated with the parotid salivary gland: one superficial, one within, and one deep to the gland.[1] These are true lymph nodes possessing both subcapsular and medullary sinusoids and having afferent and efferent lymphatics.[2] Neisse[3] demonstrated numerous true lymph nodes in the parotid gland of a 120-mm. fetus. He believed that later the nodes become encapsulated and separate from parotid tissue to form preparotid nodes, some of them containing salivary tissue. In an examination of the parotid glands of 14 newborn infants, he found an average of from 8 to 14 lymph nodes in each parotid, with salivary tissue in every one. Bernier and Bhaskar[2] reported 11 cases of ectopic salivary gland tissue in lymph nodes. They applied the term *benign lymphoepithelial cyst* to these cases.

The ectopic salivary tissue in lymph nodes can give rise to a variety of lesions characterized by pathologic changes in both the epithelial and the lymphoid tissue. Godwin[4] proposed the general term *benign lymphoepithelial lesion* for these cases. In an exhaustive review of the subject, based upon the examination of 186 case records from the Armed Forces Institute of Pathology, Bernier and Bhaskar[2] presented convincing evidence that the following benign tumors arise in ectopic salivary gland tissue in lymph nodes both within and outside the parotid gland.

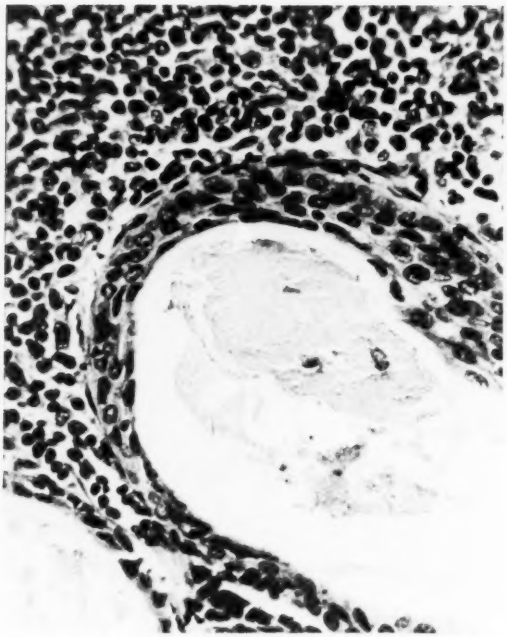

Fig. 3. Photomicrograph of a section of a cervical lymph node, showing the characteristic squamous epithelial lining of one of the cysts. Hematoxylin-eosin—methylene blue stain; magnification X 430.

I. Single or multiple cysts in lymph nodes (benign lymphoepithelial cyst)
II. Papillary cystadenoma lymphomatosum (Warthin's tumor)
III. Adenoma lymphomatosum
IV. Mixed tumor in lymph nodes (pleomorphic adenoma lymphomatosum)

They based their conclusions upon the fact that many parotid and cervical lymph nodes contain ectopic acinar and ductal elements of salivary tissue. The case for papillary cystadenoma lymphomatosum is based on the demonstration of lymph node structure in uninvolved areas of the lesion, and on the occurrence in other locations of tumors that have an identical epithelial component but lack the lymphocytic element. The same authors[5] suggest that branchial cysts that are not connected to the skin or the pharynx may arise from ectopic epithelial tissue in cervical lymph nodes.

Our cases are in group I of the Bernier and Bhaskar[2] classification of benign lymphoepithelial lesions. We have presented these cases because of the rarity of the lesion and also to point out the significance of the finding of ectopic salivary gland tissue in a lymph node.

Summary

1. Lymph nodes of the parotid salivary gland and other cervical areas may contain ectopic salivary gland tissue.

2. Benign cystic and solid lymphoepithelial tumors may occur in such lymph nodes.

3. Two cases of benign lymphoepithelial cysts (ectopic salivary gland tissue) in submaxillary lymph nodes are presented.

References

1. Gray, H.: Anatomy of the Human Body. 25th ed., edited by C. M. Goss. Philadelphia: Lea & Febiger, 1948, 1478 pp., p. 703.

2. Bernier, J. L., and Bhaskar, S. N.: Lymphoepithelial lesions of salivary glands; histogenesis and classifications based on 186 cases. Cancer **11:** 1156-1179, 1958.

3. Neisse, R.: Ueber den Einschluss von Parotisläppchen in Lymphknoten. Anat. Hefte (Wiesb.) **10:** 287-306, 1898.

4. Godwin, J. T.: Benign lymphoepithelial lesion of parotid gland (adenolymphoma, chronic inflammation, lymphoepithelioma, lymphocytic tumor, Mikulicz disease); report of 11 cases. Cancer **5:** 1089-1103, 1952.

5. Bhaskar, S. N., and Bernier, J. L.: Histogenesis of branchial cysts; report of 468 cases. Am. J. Path. **35:** 407-423, 1959.

RECENT PUBLICATIONS BY MEMBERS OF THE STAFF

AKUTSU, T.; DREYER, B.,[1] and KOLFF, W. J.: Polyurethane artificial heart valves in animals. J. Appl. Physiol. **14:** 1045-1048, Nov. 1959.

BROWN, C. H.: Duodenal ulcer complicated by obstruction; results of medical treatment. Am. J. Digest. Dis. **4:** 940-949, Nov. 1959.

BROWN, C. H.: Therapeutic principles in management of peptic ulcer; 4. Radiation therapy with cobalt-60. Am. J. Digest. Dis. (New Ser.) **4:** 1066-1072, Dec. 1959.

BROWN, C. H., and STRITTMATTER, W. C.: Postbulbar duodenal obstruction. A. M. A. Arch. Surg. **79:** 999-1003, Dec. 1959.

CAHILL, J. J., and KOLFF, W. J.: Hemolysis caused by pumps in extracorporeal circulation (in vitro evaluation of pumps). J. Appl. Physiol. **14:** 1039-1044, Nov. 1959.

CORCORAN, A. C.,[2] and PAGE, I. H.: Low Blood Pressure. The American Medical Association, 1959, 13-p. pamphlet.

CRILE, GEORGE, JR.: Carcinoma of the thyroid in children. Ann. Surg. **150:** 959-964, Dec. 1959.

DEWOLFE, V. G.: Surgery of major blood vessels: standards of care. Cleveland-Marshall Law Rev. **8:** 504-515, Sept. 1959.

DUSTAN, HARRIET P., and POUTASSE, E. F.: Diagnosis of Renal Hypertension. Pp. 167-170; discussion, 171-180, *in* Hypertension; the First Hahnemann Symposium on Hypertensive Disease, edited by J. H. Moyer. Philadelphia: W. B. Saunders Co., 1959, 790 pp.

EFFLER, D. B.; KOLFF, W. J., and GROVES, L. K.: Case history. Complications peculiar to open heart surgery; case number 15; report of a case. (Pp. 493-495.) Complications peculiar to open heart surgery. (Pp. 495-502.) Anesth. & Analg. **38:** 493-502, Nov.-Dec. 1959.

GARDNER, W. J.: Discussion of Dersh, J., and Schlezinger, N. S.: Inferior nasal quadrantanopia in pseudotumor cerebri. Tr. Am. Neurol, A.: 116-118; 117-118, 1959.

GARDNER, W. J., and MIKLOS, M.: Demonstrations. Anatomic features common to myelomeningocele of infancy and syringomyelia of adulthood. Tr. Am. Neurol. A.: 206, 1959.

GROVES, L. K., and EFFLER, D. B.: Problems in the surgical management of coarctation of the aorta. J. Thoracic & Cardiovascular Surg. **39:** 60-85; discussion, 85-90, Jan. 1960.

HALE, D. E.: The circulation in relation to newer technics in anesthesia. J. Am. A. Nurse Anesthetists **28:** 37-44, 60, Feb. 1960.

[1] *Formerly Research Associate.*
[2] *Formerly Member of the Staff.*

HAZARD, J. B.: Small papillary carcinoma of the thyroid; a study with special reference to so-called nonencapsulated sclerosing tumor. Lab. Invest. **9:** 86-97, Jan.-Feb. 1960.

HOERR, S. O.: Editorial. Elective surgery for duodenal ulcer—a graded approach. Am. J. Surg. **99:** 4-5, Jan. 1960.

KRIEGER, J. S., and McCORMACK, L. J.: Scientific exhibit. Cervical carcinoma in situ—the role of radical conization. Postgrad. Med. **27:** 99-103, Jan. 1960.

KRUSE, R. D.; KRUSE, ALICE, and BRITTON, R. C.: Physical therapy for the patient with peripheral edema: procedures for management. Phys. Therap. Rev. **40:** 29-33, Jan. 1960.

MASSON, G. M. C., and CORCORAN, A. C.[3]: High Arterial Pressure as a Primary Cause of Hypertensive Vascular Lesions. Pp. 88-95, *in* Hypertension; the First Hahnemann Symposium on Hypertensive Disease, edited by J. H. Moyer. Philadelphia: W. B. Saunders Co., 1959, 790 pp.

McCULLAGH, E. P.: Hormones—whence and whither; presidential address. J. Clin. Endocrinol. **19:** 1563-1574, Dec. 1959.

OMAE, T., and MASSON, G. M. C.: Reversibility of renal atrophy caused by unilateral reduction of renal blood supply. J. Clin. Invest. **39:** 21-27, Jan. 1960.

O'MARA, T. F.,[4] and FAULKNER, W. R.: Magnetic mixing in microtitrations. Am. J. Clin. Path. **33:** 152-155, Feb. 1960.

PAGE, I. H.: (Revision) Chap. 26, Arterial Hypertension. *In* Stroud, W. D., and Stroud, M. W.: Diagnosis and Treatment of Cardiovascular Disease. Philadelphia: F. A. Davis Co., Pub., 1959. Pp. 603-638A replace former pp. 603-638.

PAGE, I. H., and LEWIS, LENA, A.: Lipoproteins, cholesterol and serum proteins as predictors of myocardial infarction. Circulation **22:** 1011-1027, Dec. 1959.

PAGE, I. H., and SCHNECKLOTH, R. E.[5]: Hypocholesteremic effect of Benzmalacene. Circulation **22:** 1075-1078, Dec. 1959.

PAGE, I. H.; WOLFORD, R. W.,[6] and CORCORAN, A. C.[3]: Pharmacological and clinical observations on 1-(2-methoxyphenyl piperazine). Arch. internat. pharmacodyn. **119:** 214-224, March 1, 1959.

PHALEN, G. S.; McCORMACK, L. J., and GAZALE, W. J.[6]: Chap. 14. Giant-Cell Tumor of Tendon Sheath (Benign Synovioma) in the Hand; Evaluation of 56 Cases. Clin. Orthop. **15:** 140-151, Winter 1959.

[3] *Formerly Member of the Staff.*
[4] *Formerly Micro Chemist; present address: Southside District Hospital, Mesa, Arizona.*
[5] *Formerly Member of the Assistant Staff.*
[6] *Formerly Fellow.*

POUTASSE, E. F., and DUSTAN, HARRIET P.: Surgical Treatment of Renal Hypertension. Pp. 630-632, *in* Hypertension; the First Hahnemann Symposium on Hypertensive Disease, edited by J. H. Moyer. Philadelphia: W. B. Saunders Co., 1959, 790 pp.

SCHERBEL, A. L., and HARRISON, J. W.: Scientific Exhibit. Chemotherapy in rheumatoid arthritis. Postgrad. Med. **26:** 857-864, Dec. 1959.

SCHOTZ, M., and PAGE, I. H.: Effect of norepinephrine and epinephrine on nonesterified fatty acid concentration in plasma. (25039). Proc. Soc. Exper. Biol. & Med. **101:** 624-626, Aug.-Sept. 1959.

SKILLERN, P. G.: Hyperthyroidism; method of Penn G. Skillern, M.D. Pp. 344-348, *in* Current Therapy, edited by H. F. Conn. Philadelphia: W. B. Saunders Co., 1960, 808 pp.

TAPIA, F. A.,[7] and PROUDFIT, W. L.: Secondary R waves in right precordial leads in normal persons and in patients with cardiac disease. Circulation **21:** 28-37, Jan. 1960.

VAN ORDSTRAND, H. S.: The causes and management of acute and chronic respiratory acidosis. (Abs.) J. Kansas City Southwest Clin. Soc.: 16, Dec. 1959.

---

[7] *Formerly Fellow; present address: Edgewater Hospital, 5700 Ashland Avenue, Chicago 26, Illinois.*

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

affiliated with

THE CLEVELAND CLINIC FOUNDATION

announces the following postgraduate courses

Clinical Chemistry *(Sponsored by the American Association of Clinical Chemists, Cleveland Section)* . . . . . November 9, 10, and 11, 1960

Newer Developments in Ophthalmology . . . . . December 7 and 8, 1960

Upper Gastrointestinal Tract Surgery . . . . . January 11 and 12, 1961

Applications for registration are being accepted now.
Please communicate with

EDUCATION SECRETARY
THE FRANK E. BUNTS EDUCATIONAL INSTITUTE
2020 EAST 93 STREET
CLEVELAND 6, OHIO

Change of Address . . .

If you have changed your
permanent address, kindly
let us know on this form.

(Please type or print)

Name_____

Former address_____

_____

_____

New address_____

_____

_____

Cleveland Clinic Quarterly
2020 East 93 Street
Cleveland 6, Ohio